PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
FP2649 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/04031	06/12/1999	05/12/1998
International Patent Classification (IPC) or national classification and IPC C07B53/00		
Applicant UNIVERSITY OF DURHAM et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30/05/2000	03.04.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Sen, A Telephone No. +49 89 2399 8328

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/04031

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-33 as originally filed

Claims, No.:

1-14 with telefax of 26/02/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☐ claims Nos. .

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 9 and 12 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8
	No:	Claims	10,11,13 and 14; for 9 and 12 please see separate sheet
Inventive step (IS)	Yes:	Claims	1-8
	No:	Claims	10,11,13 and 14; for 9 and 12 please see separate sheet
Industrial applicability (IA)	Yes:	Claims	1-14

No: Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

D1: JP 09 143173 A

D2: DE 25 38 424 A

D3: HINTERMANN, TOBIAS ET AL: 'A useful modification of the Evans auxiliary. 4-Isopropyl-5,5- diphenyloxazolidin-2-one' HELV. CHIM. ACTA (1998), 81(11), 2093-2126

D4: CHEMICAL ABSTRACTS SERVICE: Xiao-Wu et al: 'Convenient synthesis of (S)-.alpha.,.alpha.'-diphenyl-2-pyrrolidinemethanol' retrieved from STN Database accession no. 127:278113 (1997), 911-913 ,

D5: GIBSON C L ET AL: 'A Study of 4-Substituted 5,5-Diaryl Oxazolidin-2-ones as Efficacious Chiral Auxiliaries' TETRAHEDRON LETTERS,, vol. 39, no. 37, (1998), pages 6733-6736

D6: TAMURA O ET AL: 'SYNTHETIC STUDIES ON THE KEY COMPONENT OF THE NEW GENERATION OF QUINOLONECARBOXYLIC ACID, DU-6859 1. SYNTHESIS OF (1R,2S)-2-FLUOROCYCLOPROPYLAMINE BY THE USE OF OPTICAL RESOLUTION' TETRAHEDRON vol. 50, no. 13, 28 March 1994, pages 3889-3904

D7: BAILEY D J ET AL: 'A short synthesis of (S)-2-(diphenylmethyl)pyrrolidine, a chiral solvating agent for NMR analysis' TETRAHEDRON: ASYMMETRY, vol. 8, no. 1, 9 January 1997 (1997-01-09), pages 149-153

D8: RAO, A. V. RAMA ET AL: 'Enantioselective catalytic reduction of ketones with new four-membered oxazaborolidines: application to (S)-tetramisole' TETRAHEDRON: ASYMMETRY (1992), 3(7), 859-62

D9: GAWLEY, ROBERT E. ET AL: '1-Magnesiotetrahydroisoquinolyloxazolines as Chiral Nucleophiles in Stereoselective Additions to Aldehydes: Auxiliary Optimization, Asymmetric Synthesis of (+)-Corlumine, (+)-Bicuculline, (+)-Egenine, and (+)-Corytensine, and Preliminary 13C NMR Studies of 1-Lithio- and 1-Magnesiotetrahydroisoquinol' J. ORG. CHEM. (1996), 61(23), 8103-8112

D10: DELAUNAY, D: 'A new route to oxazolidinones' J. CHEM. SOC., PERKIN TRANS. 1 (1994), (20), 3041-2

D11: ALVERNHE, GERARD ET AL: 'Fluorination of amino alcohols and hydroxyaziridines by Olah's reagent' J. CHEM. RES., SYNOP. (1983), (10), 246-7

D12: WADE, TAMSIR N.: 'Preparation of fluoro amines by the reaction of aziridines with hydrogen fluoride in pyridine solution' J. ORG. CHEM. (1980), 45(26), 5328-33

D13: ALVERNHE, G. ET AL: 'Synthesis of.alpha.,.beta.-fluoro amines and.alpha.-fluoro ketones by action of hydrofluoric acid on aziridines and azirines' TETRAHEDRON LETT. (1978), (52), 5203-6

D14: KNOLKER H -J ET AL: 'Synthesis of Chiral Oxazolidin-2-ones and Imidazolidin-2-ones via DMAP-Catalyzed Isocyanation of Amines with Di-tert-butyl Dicarbonate' TETRAHEDRON LETT., vol. 39, no. 51, 1998, pages 9407-9410

D15: O'HAGAN D ET AL: 'A short synthesis of (S)-alpha-(diphenylmethyl)alkyl amines from amino acids' TETRAHEDRON: ASYMMETRY, vol. 10, no. 6, (1999), pages 1189-1192

SECTIONS V, VII and VIII :

With regard to claims 1-8:

The subject-matter of the set of claims 1-8 directed to a process for the preparation of enantiomerically pure compounds of the general formula (I) meets the requirements of Article 33(2) PCT since the prior art documents cited in the International Search Report do not describe the preparation of these compounds of formula (I) wherein Z is H or F and A an enantiomeric CH centre by the reaction of a compound of general formula (II) with either a source of hydrogen in the presence of a hydrogenation catalyst and a catalytic support under the conditions detailed in claim 1 for the preparation of compounds wherein Z is H, or with a source of fluorine under the conditions detailed in claim 1 for the preparation of compounds wherein Z is F.

Claim 1 with regard to the hydrogenation is also considered inventive over the more

relevant documents D3 and D7 as these do not disclose or suggest the reaction of the monocyclic oxazolidinone-type compounds of general formula (II) to form primary amines or non cyclic amines as presently claimed under process conditions which in fact prolong the hydrogenation reaction time to 43-93 hours.

With regard to the fluorination, this reaction is also considered to meet the requirements of Art. 33(3) PCT since the more relevant documents D11 and D12 teach the fluorination reaction of aziridines to compounds of formula 1 but not starting from oxazolidone precursors [see for example D12, page 5330, e.g. example 1n].

With regard to this set of claims the following points are noted:

a) Clarification is required with regard to the expression "elevated pressure in the range 1-10 atm". In fact the use of this expression in connection with a pressure of 1 atm appears unclear. Please note also that the unit of pressure employed in claim 1 is not additionally expressed in terms of the units stipulated by Rule 10.1/(a)/and/(b) PCT.

b) As it is appreciated that an actual effort is being made in meeting the objections raised under Article 6 PCT for claim 1, the following should be mentioned after careful consideration of all three "alternatives" filed with regard to the reaction period mentioned in claim 1. Thus the amendment filed by inserting the tecnical feature "for a period in the range 43 to 93 hours" could be considered acceptable as it would find a clear basis in the examples of the application and moreover would point out the importance of a longer operative time required for positively carrying out the process as claimed.

With regard to claims 9 and 12:

1. Claim 9 meets an objection under Article 6 PCT. The claim is directed to a "process for preparation of a compound of the formula (I) which is a process for the preparation of enantiomerically pure polymer comprising a repeating unit of the formula (Ii)". The formulation of the claim is unclear and moreover no technical information is provided relating to the process.
2, It is not evident from the description of the application to what extent such process claim is supported in the whole extension of its definition. That is, not only it is unclear

but there is no concrete support for the subject-matter claimed in the application as originally filed.

3. Claim 12 meets an objection under Article 6 PCT and should thus be clarified at the light of art least one concrete example on the description.

With regard to claim 10:

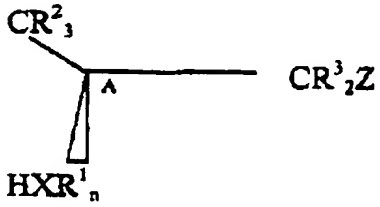
From the description of the application on page 6, line 12 to page 7, line 7 it is described that the reaction of compound of formula (IV) with a compound of formula (V) results in a compound of formula (III). This reaction is known in the art as well the cyclisation of the amino alcohol intermediate (III) with trichloromethyl chloroformate (see for example also D5, Scheme I) to afford a oxazolidione compound. Accordingly. first of all the present formulation of the claim is not supported by the description of the application as originally filed and secondly, it describes subject-matter known in the art. Accordingly, the requirements of patentability under Art. 33(2) and (3) PCT are not met.

With regard to claims 11 as well as 13 and 14:

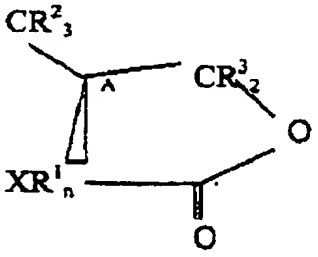
Claim 11 comprises subject-matter described in the art and meets therefore an objection under Article 33(2) PCT [see for example document D12, compound 6E wherein R is CH_3]. The inventive step for the compounds claimed is also not evident as similar compounds are described in the art, for example as useful intermediates in synthetic applications.

CLAIMS

1. Process for the preparation of enantiomerically pure compounds of formula I:

(I) 

comprising contacting a compound of formula II:

(II) 

with a source of hydrogen at ambient temperature and elevated pressure in the range 1 – 10 atm for a period *which is other than 2 hours or less (proviso taking basis from D3); alternatively for a period of 43 hours (taking basis from Examples); alternatively for a period in the range 43 to 93 hours (taking basis from examples)* in the presence of a hydrogenation catalyst which is homogeneous or heterogeneous and comprises a metal selected from the transition metals of Group VIII of the Periodic Table of the Elements and a catalytic support; or

with a source of fluorine as a fluorination agent which comprises gaseous or liquid phase HF and a carrier, at temperature in the range 0 – 20C and ambient pressure for a period of 24 hours

wherein A is an *enantiomerically pure* centre *CH*; Z is hydrogen or *fluoro*

X is selected from oxygen, sulphur and nitrogen and n is selected from 0 and 1 and is equal to the valence of X less 2; and R^1 to R^3 are as defined below

and wherein each R^1 is independently selected from hydrogen or from straight chain or branched, saturated or unsaturated C_{1-8} hydrocarbon optionally substituted by one or more hydroxy, halo, aryl, cyclo C_{1-8} alkyl;

each R^3 is independently selected from hydrogen or halo; and straight and branched chain, saturated and unsaturated C_{1-4} alkyl, alkenyl and alkynyl and aryl;
each optionally substituted by hydroxy, halo, saturated or unsaturated C_{1-4} alkyl, alkenyl or alkynyl, aryl, cyclo C_{1-6} alkyl, carbonyl, carboxyl, amino, amido;

each R^2 is independently selected from hydrogen, straight chain and branched, saturated and unsaturated C_{1-8} alkyl, optionally substituted by hydroxy, halo, aryl, cyclo C_{1-6} alkyl, carbonyl, carboxyl, amino, amido.

2. Process as claimed in Claim 1 wherein X is nitrogen whereby n is 1.

3. Process as claimed in any one of Claims 1 and 2 wherein R^3 is selected from ethenyl, ethynyl and optionally substituted phenyl.

4. Process as claimed in any one of Claims 1-3 wherein at least one and preferably both of R^3 are aryl.

5. Process as claimed in any one of Claims 1-4 wherein R^2 is selected from optionally hydroxy, halo or alkoxy substituted branched and straight chain C_{1-6} alkyl, including methyl, ethyl, i-propyl, i-butyl, t-butyl; and aryl including phenyl and benzyl.

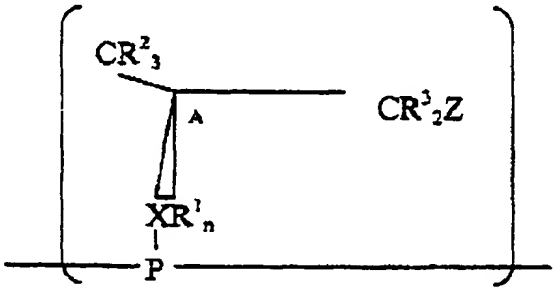
6. Process as claimed in any one Claims 1 to 5 wherein X is nitrogen wherein n is 1 and R^1 is H, i.e. the compound is a primary amine.

7. Process as claimed in any one of Claims 1-6 wherein a catalyst comprises Pd with C as catalytic support.

8. Process as claimed in any of Claims 1-7 wherein a fluorination agent is liquid phase HF-pyridine.

9 [13,14[16,17]]. *Process for preparation of a compound of the formula I as hereinbefore defined in any of Claims 1 to 8 which is a process for the* preparation of enantiomerically pure enantiomerically pure polymer comprising a repeating unit of the formula Ii:

(Ii)

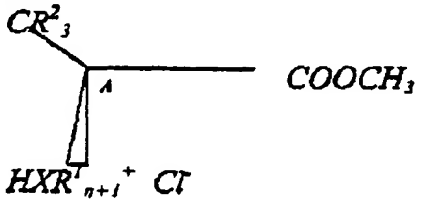


wherein P is derived from a polymerisable monomer or oligomer and X, R^1, R^2, R^3, Z and A are as hereinbefore defined in any of Claims 1 to 6; and

wherein a polymerisable monomer is selected from the group consisting of: an epoxy resin; an addition-polymerisation resin; a formaldehyde condensate resin; a cyanate resin; and an isocyanate resin; polyaromatics; monomers of natural polymers including carbohydrates, polypeptides and proteins including starch, celluloses, collagen, gelatin, dextrans, alginates, chitin and chitosan; and monomers of biodegradeable and/or biocompatible polymers including poly(lactic acid), poly(glycolic acid), polycaprolactone, polyorthoesters, polyanhydrides, polyaminoacids and azo polymers; and mixtures thereof.

10 [17,18[20,21]]. *Process for preparation of enantiomerically pure compounds of formula I as hereinbefore defined in any of Claims 1 to 8 which is a process for the* preparation of a library of compounds comprising:

reacting one or more compounds of formula IV

(IV) 

Wherein *R^1, R^2 and A are as hereinbefore defined in any of Claims 1 to 6*

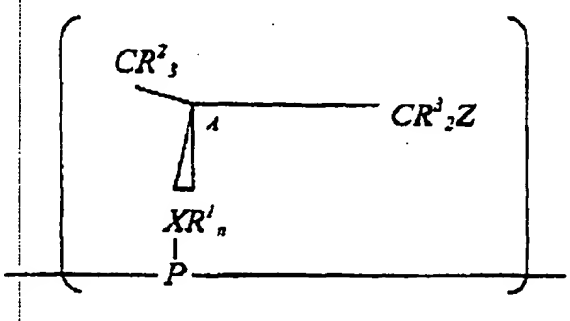
with a plurality of compounds of formula V R^2MgBr, and converting via compounds of formula II as hereinbefore defined *in Claim 1 to 6* to compounds of formula I as hereinbefore defined *in any of Claims 1 to 6*; and

optionally labelling the support or vessel with means to identify the synthetic history of the supported or contained compound.

11 [12]. *Enantiomerically pure* compound of the formula I as hereinbefore defined in any of Claims 1 to 6 wherein A, Z and R^1 to R^3 are as hereinbefore defined, X is N and n is 1.

12 [15[18]]. *Enantiomerically pure polymer comprising a repeating unit of the formula Ii:*

(Ii)



wherein *P is derived from a polymerisable monomer or oligomer selected from the group consisting of: an epoxy resin; an addition-polymerisation resin; a formaldehyde condensate resin; a cyanate resin; and an isocyanate resin; polyaromatics; monomers of natural polymers including carbohydrates, polypeptides and proteins including starch, celluloses, collagen, gelatin, dextrans, alginates, chitin and chitosan; and monomers of biodegradeable and/or biocompatible polymers including poly(lactic acid), poly(glycolic acid), polycaprolactone, polyorthoesters; and*

X, R^1, R^2, R^3, Z and A are as hereinbefore defined in any of Claims 1 to 6.

13 [19 [22]]. Library of enantiomerically pure compounds of formula I as hereinbefore defined *in Claim 11*.

14 [20 [23]]. Pharmaceutical, veterinary product or agrochemical composition comprising an enantiomerically pure compound of formula I, Ii or Iii as hereinbefore defined *in any of Claims 11 - 13* with suitable diluents, adjuvants, carriers.

INTERNATIONAL SEARCH REPORT

[redacted] al Application No
PCT/GB 99/04031

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07B53/00 C07C209/68 C07C211/27 C07C211/29 C07D207/10
C07B61/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07B C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 09 143173 A (SHIRATORI PHARMACEUTICAL CO., LTD., JAPAN) 3 June 1997 (1997-06-03) page 3-4	13,15
X	HINTERMANN, TOBIAS ET AL: "A useful modification of the Evans auxiliary. 4-Isopropyl-5,5- diphenyloxazolidin-2-one" HELV. CHIM. ACTA (1998), 81(11), 2093-2126 , XP002134506 page 2093 -page 2095	1,13,15
X	* see on page 2099 footnote 16) *	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 April 2000	17/04/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bader, K

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GIBSON C L ET AL: "A Study of 4-Substituted 5,5-Diaryl Oxazolidin-2-ones as Efficacious Chiral Auxiliaries" TETRAHEDRON LETTERS,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 39, no. 37, 10 September 1998 (1998-09-10), pages 6733-6736, XP004132590 ISSN: 0040-4039 page 6734	13,15

X	TAMURA O ET AL: "SYNTHETIC STUDIES ON THE KEY COMPONENT OF THE NEW GENERATION OF QUINOLONECARBOXYLIC ACID, DU-6859 1. SYNTHESIS OF (1R,2S)-2-FLUOROCYCLOPROPYLAMINE BY THE USE OF OPTICAL RESOLUTION" TETRAHEDRON.NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 50, no. 13, 28 March 1994 (1994-03-28), pages 3889-3904, XP000575878 ISSN: 0040-4020 cited in the application page 3906	13
A	page 3913	1

X	BAILEY D J ET AL: "A short synthesis of (S)-2-(diphenylmethyl)pyrrolidine, a chiral solvating agent for NMR analysis" TETRAHEDRON: ASYMMETRY,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 8, no. 1, 9 January 1997 (1997-01-09), pages 149-153, XP004015186 ISSN: 0957-4166 cited in the application	1-3,5-9, 11-15
X	PREPARATION OF COMPOUND 4 ON PAGE 151	1

X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US YANG, XIAO-WU ET AL: "Convenient synthesis of (S)-.alpha.,.alpha.'-diphenyl-2-pyrrolidinemethanol" retrieved from STN Database accession no. 127:278113 XP002134513 abstract & GAODENG XUEXIAO HUAXUE XUEBAO (1997), 18(6), 911-913 ,	13,15

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RAO, A. V. RAMA ET AL: "Enantioselective catalytic reduction of ketones with new four-membered oxazaborolidines: application to (S)-tetramisole" TETRAHEDRON: ASYMMETRY (1992), 3(7), 859-62 , XP002134507 the whole document	13
X	GAWLEY, ROBERT E. ET AL: "1-Magnesiotetrahydroisoquinolyloxazolines as Chiral Nucleophiles in Stereoselective Additions to Aldehydes: Auxiliary Optimization, Asymmetric Synthesis of (+)-Corlumine, (+)-Bicuculline, (+)-Egenine, and (+)-Corytensine, and Preliminary 13C NMR Studies of 1-Lithio- and 1-Magnesiotetrahydroisoquinol" J. ORG. CHEM. (1996), 61(23), 8103-8112 , XP002134508 cited in the application SEE THE EXAMPLES	13,15
X	DELAUNAY, DOMINIQUE ET AL: "A new route to oxazolidinones" J. CHEM. SOC., PERKIN TRANS. 1 (1994), (20), 3041-2 , XP002134509 the whole document	13,15
X	DE 25 38 424 A (NORDMARK WERKE GMBH) 3 March 1977 (1977-03-03) SEE THE EXAMPLES	13,15
X	ALVERNHE, GERARD ET AL: "Fluorination of amino alcohols and hydroxyaziridines by Olah's reagent" J. CHEM. RES., SYNOP. (1983), (10), 246-7 , XP002134510	13,15
A	the whole document	1
X	WADE, TAMSIR N.: "Preparation of fluoro amines by the reaction of aziridines with hydrogen fluoride in pyridine solution" J. ORG. CHEM. (1980), 45(26), 5328-33 , XP002134511	13,15
A	page 5330	1
X	ALVERNHE, G. ET AL: "Synthesis of.alpha.,.beta.-fluoro amines and.alpha.-fluoro ketones by action of hydrofluoric acid on aziridines and azirines" TETRAHEDRON LETT. (1978), (52), 5203-6 , XP002134512	13,15
A	page 5204	1

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INTERNATIONAL SEARCH REPORT

[redacted] ...al Application No
[redacted] GB 99/04031

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	KNOLKER H -J ET AL: "Synthesis of Chiral Oxazolidin-2-ones and Imidazolidin-2-ones via DMAP-Catalyzed Isocyanation of Amines with Di-tert-butyl Dicarbonate" TETRAHEDRON LETTERS,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 39, no. 51, 17 December 1998 (1998-12-17), pages 9407-9410, XP004144213 ISSN: 0040-4039 page 9408 ---	13,15
X,P	O'HAGAN D ET AL: "A short synthesis of (S)-alpha-(diphenylmethyl)alkyl amines from amino acids" TETRAHEDRON: ASYMMETRY,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 10, no. 6, 26 March 1999 (1999-03-26), pages 1189-1192, XP004164869 ISSN: 0957-4166 the whole document -----	1-23

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/04031

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 99 /04031

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-23 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search over the whole breadth of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely Compounds of formula I with X=N, n=1 and B= -C(Ph)2 and Z= -F; as supported by the description on pages 29-31.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

[redacted]tion on patent family members

[redacted]al Application No
PCT/GB 99/04031

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 9143173 A	03-06-1997	NONE	
DE 2538424 A	03-03-1977	AT 347453 B	27-12-1978
		AT 619876 A	15-05-1978
		AU 506441 B	03-01-1980
		AU 1614576 A	26-01-1978
		BE 845581 A	16-12-1976
		CA 1072567 A	26-02-1980
		CH 623043 A	15-05-1981
		DK 387876 A	01-03-1977
		FI 762400 A,B,	01-03-1977
		FR 2321884 A	25-03-1977
		GB 1555658 A	14-11-1979
		HU 174488 B	28-01-1980
		IE 43396 B	11-02-1981
		IL 50091 A	30-01-1981
		IN 144061 A	18-03-1978
		JP 1064501 C	22-09-1981
		JP 52053857 A	30-04-1977
		JP 56004554 B	30-01-1981
		LU 75659 A	31-03-1977
		NL 7609559 A	02-03-1977
		NO 762928 A,B,	01-03-1977
		SE 424991 B	23-08-1982
		SE 7609426 A	01-03-1977
		US 4139538 A	13-02-1979
		US 4179442 A	18-12-1979
		ZA 7604279 A	27-07-1977

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
FP2649		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 99/04031	06/12/1999	05/12/1998
Applicant		
UNIVERSITY OF DURHAM et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/04031

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-23 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search over the whole breadth of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely Compounds of formula I with X=N, n=1 and B= -C(Ph)2 and Z= -F; as supported by the description on pages 29-31.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
P[redacted]B 99/04031

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07B53/00 C07C209/68 C07C211/27 C07C211/29 C07D207/10
C07B61/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07B C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 09 143173 A (SHIRATORI PHARMACEUTICAL CO., LTD., JAPAN) 3 June 1997 (1997-06-03) page 3-4 ---	13,15
X	HINTERMANN, TOBIAS ET AL: "A useful modification of the Evans auxiliary. 4-Isopropyl-5,5- diphenyloxazolidin-2-one" HELV. CHIM. ACTA (1998), 81(11), 2093-2126 , XP002134506 page 2093 -page 2095	1,13,15
X	* see on page 2099 footnote 16) * --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 April 2000	17/04/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bader, K

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GIBSON C L ET AL: "A Study of 4-Substituted 5,5-Diaryl Oxazolidin-2-ones as Efficacious Chiral Auxiliaries" TETRAHEDRON LETTERS,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 39, no. 37, 10 September 1998 (1998-09-10), pages 6733-6736, XP004132590 ISSN: 0040-4039 page 6734	13,15
X	TAMURA O ET AL: "SYNTHETIC STUDIES ON THE KEY COMPONENT OF THE NEW GENERATION OF QUINOLONECARBOXYLIC ACID, DU-6859 1. SYNTHESIS OF (1R,2S)-2-FLUOROCYCLOPROPYLAMINE BY THE USE OF OPTICAL RESOLUTION" TETRAHEDRON,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 50, no. 13, 28 March 1994 (1994-03-28), pages 3889-3904, XP000575878 ISSN: 0040-4020 cited in the application page 3906	13
A	page 3913	1
X	BAILEY D J ET AL: "A short synthesis of (S)-2-(diphenylmethyl)pyrrolidine, a chiral solvating agent for NMR analysis" TETRAHEDRON: ASYMMETRY,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 8, no. 1, 9 January 1997 (1997-01-09), pages 149-153, XP004015186 ISSN: 0957-4166 cited in the application	1-3,5-9, 11-15
X	PREPARATION OF COMPOUND 4 ON PAGE 151	1
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US YANG, XIAO-WU ET AL: "Convenient synthesis of (S)-.alpha.,.alpha.'-diphenyl-2-pyrrolidinemethanol" retrieved from STN Database accession no. 127:278113 XP002134513 abstract & GAODENG XUEXIAO HUAXUE XUEBAO (1997), 18(6), 911-913 ,	13,15

-/--

1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	RAO, A. V. RAMA ET AL: "Enantioselective catalytic reduction of ketones with new four-membered oxazaborolidines: application to (S)-tetramisole" TETRAHEDRON: ASYMMETRY (1992), 3(7), 859-62 , XP002134507 the whole document	13
X	GAWLEY, ROBERT E. ET AL: "1-Magnesiotetrahydroisoquinolyloxazolines as Chiral Nucleophiles in Stereoselective Additions to Aldehydes: Auxiliary Optimization, Asymmetric Synthesis of (+)-Corlumine, (+)-Bicuculline, (+)-Egenine, and (+)-Corytensine, and Preliminary 13C NMR Studies of 1-Lithio- and 1-Magnesiotetrahydroisoquinol" J. ORG. CHEM. (1996), 61(23), 8103-8112 , XP002134508 cited in the application SEE THE EXAMPLES	13,15
X	DELAUNAY, DOMINIQUE ET AL: "A new route to oxazolidinones" J. CHEM. SOC., PERKIN TRANS. 1 (1994), (20), 3041-2 , XP002134509 the whole document	13,15
X	DE 25 38 424 A (NORDMARK WERKE GMBH) 3 March 1977 (1977-03-03) SEE THE EXAMPLES	13,15
X	ALVERNHE, GERARD ET AL: "Fluorination of amino alcohols and hydroxyaziridines by Olah's reagent" J. CHEM. RES., SYNOP. (1983), (10), 246-7 , XP002134510	13,15
A	the whole document	1
X	WADE, TAMSIR N.: "Preparation of fluoro amines by the reaction of aziridines with hydrogen fluoride in pyridine solution" J. ORG. CHEM. (1980), 45(26), 5328-33 , XP002134511	13,15
A	page 5330	1
X	ALVERNHE, G. ET AL: "Synthesis of.alpha.,.beta.-fluoro amines and.alpha.-fluoro ketones by action of hydrofluoric acid on aziridines and azirines" TETRAHEDRON LETT. (1978), (52), 5203-6 , XP002134512	13,15
A	page 5204	1

-/--

1

International Application No
[redacted]GB 99/04031

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X,P	KNOLKER H -J ET AL: "Synthesis of Chiral Oxazolidin-2-ones and Imidazolidin-2-ones via DMAP-Catalyzed Isocyanation of Amines with Di-tert-butyl Dicarbonate" TETRAHEDRON LETTERS,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 39, no. 51, 17 December 1998 (1998-12-17), pages 9407-9410, XP004144213 ISSN: 0040-4039 page 9408	13,15
X,P	O'HAGAN D ET AL: "A short synthesis of (S)-alpha-(diphenylmethyl)alkyl amines from amino acids" TETRAHEDRON: ASYMMETRY,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 10, no. 6, 26 March 1999 (1999-03-26), pages 1189-1192, XP004164869 ISSN: 0957-4166 the whole document	1-23

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
P[redacted]B 99/04031

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
JP 9143173	A	03-06-1997	NONE		
DE 2538424	A	03-03-1977	AT	347453 B	27-12-1978
			AT	619876 A	15-05-1978
			AU	506441 B	03-01-1980
			AU	1614576 A	26-01-1978
			BE	845581 A	16-12-1976
			CA	1072567 A	26-02-1980
			CH	623043 A	15-05-1981
			DK	387876 A	01-03-1977
			FI	762400 A,B,	01-03-1977
			FR	2321884 A	25-03-1977
			GB	1555658 A	14-11-1979
			HU	174488 B	28-01-1980
			IE	43396 B	11-02-1981
			IL	50091 A	30-01-1981
			IN	144061 A	18-03-1978
			JP	1064501 C	22-09-1981
			JP	52053857 A	30-04-1977
			JP	56004554 B	30-01-1981
			LU	75659 A	31-03-1977
			NL	7609559 A	02-03-1977
			NO	762928 A,B,	01-03-1977
			SE	424991 B	23-08-1982
			SE	7609426 A	01-03-1977
			US	4139538 A	13-02-1979
			US	4179442 A	18-12-1979
			ZA	7604279 A	27-07-1977

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 10 July 2000 (10.07.00)	
International application No. PCT/GB99/04031	**Applicant's or agent's file reference** FP2649
International filing date (day/month/year) 06 December 1999 (06.12.99)	**Priority date** (day/month/year) 05 December 1998 (05.12.98)
Applicant O'HAGAN, David	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

30 May 2000 (30.05.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Pascal Piriou

Telephone No.: (41-22) 338.83.38

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* FP2649

Box No. I TITLE OF INVENTION PROCESS FOR PREPARING CHIRAL COMPOUNDS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

UNIVERSITY OF DURHAM
SOUTH ROAD
DURHAM
DH1 3LE

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

O'HAGAN, DAVID
UNIVERSITY OF DURHAM
SOUTH ROAD
DURHAM
DH1 3LE

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

MARKGRAAF PATENTS LIMITED
THE CRESCENT
54 BLOSSOM STREET
YORK YO24 1AP

Telephone No. 01904 610586

Facsimile No. 01904 610909

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☒ **AP** ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ **EA** Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ **AE** United Arab Emirates
☒ **AL** Albania .....
☒ **AM** Armenia .....
☒ **AT** Austria .....
☒ **AU** Australia .....
☒ **AZ** Azerbaijan
☒ **BA** Bosnia and Herzegovina .....
☒ **BB** Barbados
☒ **BG** Bulgaria .....
☒ **BR** Brazil .....
☒ **BY** Belarus .....
☒ **CA** Canada
☒ **CH and LI** Switzerland and Liechtenstein
☒ **CN** China .....
☒ **CU** Cuba .....
☒ **CZ** Czech Republic .....
☒ **DE** Germany .....
☒ **DK** Denmark .....
☒ **EE** Estonia .....
☒ **ES** Spain .....
☒ **FI** Finland .....
☒ **GB** United Kingdom
☒ **GD** Grenada
☒ **GE** Georgia .....
☒ **GH** Ghana .....
☒ **GM** Gambia
☒ **HR** Croatia .....
☒ **HU** Hungary .....
☒ **ID** Indonesia
☒ **IL** Israel .....
☒ **IN** India .....
☒ **IS** Iceland
☒ **JP** Japan .....
☒ **KE** Kenya .....
☒ **KG** Kyrgyzstan .....
☒ **KP** Democratic People's Republic of Korea .....
☒ **KR** Republic of Korea .....
☒ **KZ** Kazakhstan .....
☒ **LC** Saint Lucia
☒ **LK** Sri Lanka
☒ **LR** Liberia
☒ **LS** Lesotho .....
☒ **LT** Lithuania
☒ **LU** Luxembourg
☒ **LV** Latvia
☒ **MD** Republic of Moldova .....
☒ **MG** Madagascar .....
☒ **MK** The former Yugoslav Republic of Macedonia .....
☒ **MN** Mongolia
☒ **MW** Malawi .....
☒ **MX** Mexico .....
☒ **NO** Norway
☒ **NZ** New Zealand .....
☒ **PL** Poland .....
☒ **PT** Portugal .....
☒ **RO** Romania
☒ **RU** Russian Federation .....
☒ **SD** Sudan
☒ **SE** Sweden
☒ **SG** Singapore
☒ **SI** Slovenia .....
☒ **SK** Slovakia .....
☒ **SL** Sierra Leone .....
☒ **TJ** Tajikistan .....
☒ **TM** Turkmenistan .....
☒ **TR** Turkey .....
☒ **TT** Trinidad and Tobago .....
☒ **UA** Ukraine .....
☒ **UG** Uganda .....
☒ **US** United States of America .....
☒ **UZ** Uzbekistan .....
☒ **VN** Viet Nam .....
☒ **YU** Yugoslavia .....
☒ **ZA** South Africa .....
☒ **ZW** Zimbabwe .....

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ DM Dominica .....
☒ TZ Tanzania .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

See Notes to the request form

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 5.12.1998	9826700.8	GB		
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): 23/77 filed

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)* : ISA/

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*
Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	:	3
description (excluding sequence listing part)	:	32
claims	:	6
abstract	:	1
drawings	:	
sequence listing part of description	:	
Total number of sheets	:	42

This international application is **accompanied by** the item(s) marked below:

1. ☐ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Markgraaf Patents Ltd

MARKGRAAF PATENTS LIMITED 6.12.1999

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA/	6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

The demand must be filed directly with the competent International Preliminary Examining Authority; if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: FP2649 WO

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/GB99/04031	06/12/99	05/12/98

Title of invention: PROCESS FOR PREPARING POLYMERS

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

UNIVERSITY OF DURHAM
OLD SHIRE HALL
DURHAM
DH1 3HP

Telephone No.:

Facsimile No.:

Teleprinter No.:

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
GB	GB

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

O'HAGAN, DAVID
UNIVERSITY OF DURHAM
SOUTH ROAD
DURHAM
DH1 3LE

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
GB	GB

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on a continuation sheet.

See Notes to the demand form

International application No.
PCT/GB99/04031

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [x] agent [ ] common representative

and [ ] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

MARKGRAAF PATENTS LIMITED
THE CRESCENT
54 BLOSSOM STREET
YORK
YO24 1AP

Telephone No.: 01904 610586

Facsimile No.: 01904 610909

Teleprinter No.:

[ ] **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special addr ess to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

[x] the international application as originally filed

the description [ ] as originally filed
[ ] as amended under Article 34

the claims [ ] as originally filed
[ ] as amended under Article 19 (together with any accompanying statement)
[ ] as amended under Article 34

the drawings [ ] as originally filed
[ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. [ ] The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

[x] which is the language in which the international application was filed.

[ ] which is the language of a translation furnished for the purposes of international search.

[ ] which is the language of publication of the international application.

[ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

Sheet No. ...3

International application No.
PCT/GB99/04031

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)* Statement (A19)	: 1	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☐ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ nucleotide and or amino acid sequence listing in computer readable form
6. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Markgraaf Patents Ltd

MARKGRAAF PATENTS LIMITED 30.05.2000

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

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Demand received from IPEA on:

Statement under A19

We refer to the International search in which the search examiner conducted his search on the basis of a narrow class of compounds as represented by Claim 1 incorporating features of Claim 2 (X = nitrogen), Claim 3 ($B{=}CPh_2$) and Claim 5 (Z = F). We submit that the search results are in fact suitable to a broader class of compounds, certainly in which Z = H or F, and request that the broader class be taken into consideration in the International Examination.

We submit that all claims are in fact novel over the cited documents, including Hintermann et al, Helvetica Chimica Acta – Vol. 81 (1998), 2093-2125 (reference 16 at page 2099 structure at page 2100) in which the disclosed compound N does not comprise a compound of formula I according to the present invention, wherein R^1 is as defined (H or $C_{1\text{-}8}$ hydrocarbon optionally substituted by one or more hydroxy, halo, aryl, cyclo $C_{1\text{-}8}$ alkyl) – in the cited document the corresponding group is in fact a carbonyl group $COCHRCH_2NHBoc$.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07B 53/00, C07C 209/68, 211/27, 211/29, C07D 207/10, C07B 61/00

A1

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9826700.8 5 December 1998 (05.12.98) GB

(71) Applicant *(for all designated States except US)*: UNIVERSITY OF DURHAM [GB/GB]; Old shire Hall, Durham DH1 3HP (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: O'HAGAN, David [GB/GB]; University of Durham, South Road, Durham DH1 3LE (GB).

(74) Agent: MARKGRAAF PATENTS LIMITED; The Crescent, 54 Blossom Street, York YO24 1AP (GB).

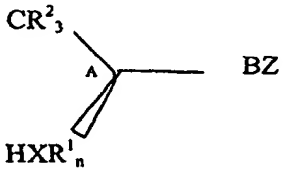
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

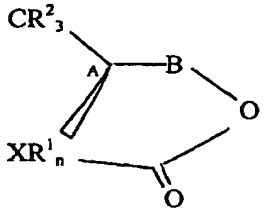
With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PROCESS FOR PREPARING CHIRAL COMPOUNDS



(I)



(II)

(57) Abstract

Process for the preparation of chiral compounds of formula (I) comprising contacting a compound of formula (II) with a source of hydrogen or halide; wherein A is a chiral centre; X is selected from oxygen, sulphur and nitrogen; n is selected from 0 and 1 and is equal to the valence of X less 2; B is a fragment CR^3_2; Z is hydrogen or halogen; with the proviso that when X is nitrogen, n is 1, one of R^1 and two of R^2 are hydrogen, BZ is $CHPh_2$, the other R^1 and R^2 do not form together a five membered heterocyclic (pyrrolidone) ring; novel intermediates, novel compounds, polymers and libraries thereof and the use thereof as fine chemicals, and compositions thereof.

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PROCESS FOR PREPARING CHIRAL COMPOUNDS

The present invention relates to a process for the preparation of a class of enantiomerically pure chiral compounds, the compounds obtained thereby and novel compounds, compositions thereof and the use thereof as or in the preparation of a pharmaceutical, veterinary product, agrochemical, polymer, library of compounds and their respective intermediates.

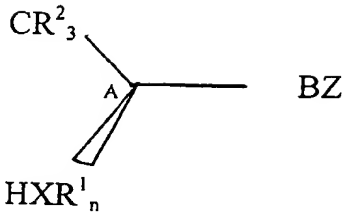
Efficient and simple synthesis of known and novel compounds can be the key to commercial success and may also lead to further development and discoveries enabled by availability of compounds in significant purities, yields and the like. Nevertheless development of new synthetic routes is costly and time consuming, without the guarantee of success.

Tet: Asymm, 1997, 8(1), 149-153 discloses the synthesis of the corresponding excluded pyrrolidine which is a known chiral compound, but makes no reference to synthesis of analogues of any class of analogues, thus implies a unique synthesis for the compound alone.

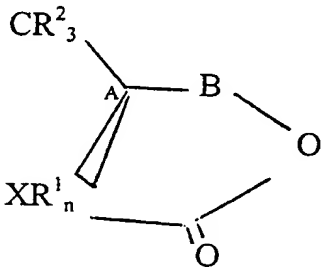
The authors have now found, according to the present invention, that the synthesis is effective for a distinct class of compounds having potential as or in the preparation of organic fine chemicals and polymers.

We have now surprisingly found a process for synthesising a class of compounds in novel manner to produce enantiomerically pure hetero compounds.

Accordingly in a first aspect there is provided a process for the preparation of chiral compounds of formula I:

(I) 

comprising contacting a compound of formula II:

(II) 

with a source of hydrogen or halide;

wherein A is a chiral centre;

X is selected from oxygen, sulphur and nitrogen;

n is selected from 0 and 1 and is equal to the valence of X less 2;

Each R^1 is independently selected from hydrogen, straight chain and branched, saturated and unsaturated C_{1-8} hydrocarbon optionally substituted by one or more hydroxy, halo, aryl, cyclo C_{1-8} alkyl and the like;

B is a fragment CR^3_2 wherein each R^3 is independently selected from hydrogen, halo, azides and cyanides; straight and branched chain, saturated and unsaturated C_{1-4} alkyl, alkenyl and alkynyl and aryl, each optionally substituted by hydroxy, halo, saturated or unsaturated C_{1-4} alkyl, alkenyl or

alkynyl, aryl, cyclo C_{1-6} alkyl, carbonyl, carboxyl, amino, amido, (thio)ether, haloalkyl, silylalkyl and the like;

Z is hydrogen or halogen;

each R^2 is independently selected from hydrogen, straight chain and branched, saturated and unsaturated C_{1-8} alkyl, optionally substituted by hydroxy, halo, aryl, cyclo C_{1-6} alkyl, carbonyl, carboxyl, amino, amido, (thio)ether and the like; and

one of R^1 and one of R^2 together may form an alkylene group as part of a heterocyclic ring;

with the proviso that when X is nitrogen, n is 1, one of R^1 and two of R^2 are hydrogen, BZ is $CHPh_2$, the other R^1 and R^2 do not form together a five membered heterocyclic (pyrrolidone) ring.

Preferably X is nitrogen whereby n is 1.

Preferably B is a fragment CR^3_2 wherein R^3 is selected from ethenyl, propenyl ethynyl and propynyl, optionally substituted phenyl, for example 4-methoxy or 4-perfluoryl alkyl phenyl, naphthyl, methyl phenyl and the like.

More preferably B is a group as hereinbefore defined wherein at least one and preferably both of R^3 are aryl, more preferably optionally substituted phenyl.

Preferably Z is selected from hydrogen, chloro and fluoro, more preferably hydrogen and fluoro.

Preferably R^2 is selected from optionally hydroxy, halo, alkoxy substituted branched and straight chain C_{1-6} alkyl, including methyl, ethyl, i-propyl, i-butyl, t-butyl; and aryl including phenyl and benzyl.

Preferably X is nitrogen wherein n is 1 and R^1 does not form a cyclic ring with one of R^2, i.e. the compound is a non cyclic secondary amine, or R^1 is H, and R^2 is other than H, i.e. the compound is a primary amine.

Without being limited to this theory it is thought that the conversion according to the process of the invention proceeds via a substitution with subsequent decarboxylation or decarboxylation with subsequent quenching.

Contacting the compound of formula II as hereinbefore defined may be in the presence of a catalyst which may be homogeneous or heterogeneous, and is preferably heterogeneous, or of an agent which may be gaseous or liquid and is preferably liquid.

The catalyst may be selected from any catalyst suitable for the conversion as hereinbefore defined. Preferably the catalyst comprises a hydrogenation or fluorination catalyst or agent. A hydrogenation catalyst suitably comprises a metal adapted to catalyse a hydrogenation reaction, for example selected from the transition metals of Group VIII of the Periodic Table of the Elements, preferably selected from Pt, Pd, Ni, Co, Cu, Ru, Fe and Ag and mixtures thereof. The catalyst may be in the form of the metal(s) or salts thereof, optionally in the presence of or including additional catalytic components or catalytic supports such as C. More preferably the catalyst

comprises palladium and carbon, and reaction is in the presence of gaseous hydrogen.

A fluorination agent suitably comprises a source of fluorine associated with an activating component adapted to facilitate fluorination reaction, for example liquid phase HF and a carrier, preferably HF-pyridine (Olah's reagent).

The catalyst or agent is present in catalytically or transformationally effective amount.

The process may be carried out with use of any additional solvents, and may be carried out at reduced, ambient or elevated temperature and/or pressure or a combination thereof in sequence. Gaseous reaction is preferably carried out at ambient temperature and elevated pressure in the range 1-10 atm and liquid phase reaction at ambient pressure and temperature in the range 0 – 20 °C.

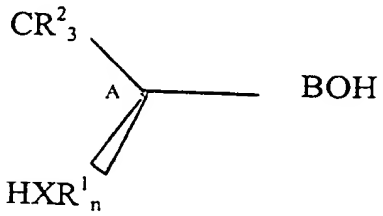
The process of the invention is preferably suitable for the preparation of pharmaceutical, veterinary product, agrochemical and polymeric compounds and libraries of such compounds, and their synthetic intermediates. It is a particular advantage of the process of the invention that such compounds may be readily prepared in which B is analogous electronically and/or sterically to characteristic groupings in known pharmaceutical, veterinary product and agrochemicals. The process therefore provides a known route to access compounds and whole ranges of new analogues, wherein the group B is as hereinbefore defined.

Alternatively the process as hereinbefore defined is suited for the preparation of metal complexes as asymmetric catalysts.

In a further aspect of the invention there is provided a class of novel enantiomerically pure chiral hetero compounds of the formula I as hereinbefore defined wherein A, B, Z and R^1 are as hereinbefore defined, X is N and n is 1 with the exception that R^2 is not phenyl or benzyl when R^1 is hydrogen, BH is phenyl or CH_3 and Z is H.

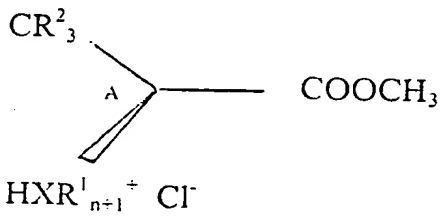
Compounds of the formula II as hereinbefore defined may be obtained commercially or prepared by known means. Akiba *et al*, Tetrahedron, 1994, 50 (13), 3905 discloses the preparation of a compound of formula II by cyclisation of amino alcohol with trichloromethyl chloroformate ($Cl_3COCOCl$) in the presence of triethylamine (Et_3N). Using this process compounds of formula II are obtained from compounds of formula III:

(III)



Intermediate compounds of formula III as hereinbefore defined may be obtained commercially or using the process, for example of Gawley and Zhang, J. Org. Chem., 1996, 61, 8103, and Itsuno *et al*, J. Chem. Soc., Perkin Trans. I, 1985, 2039. In these publications is taught the preparation of a compound of formula III as hereinbefore defined by reaction of a compound of formula IV:

(IV)



with a compound of formula V:

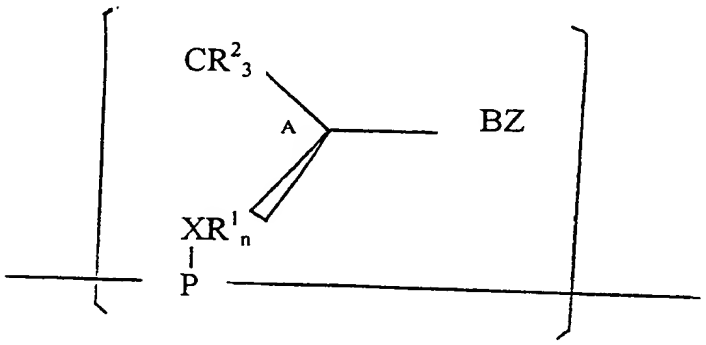
(V) R^2MgBr.

Reaction is preferably under reflux in cold solvent.

Compounds of formula IV and V are commercially available or may be synthesised by known means.

In a further aspect of the invention there is provided a process for the preparation of enantiomerically pure chiral polymers comprising a repeating unit of the formula Ii:

(Ii)



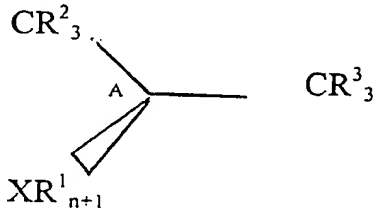
wherein P is derived from a polymerisable monomer or oligomer and X, R^1, R^2, B, Z and A are as hereinbefore defined.

Polymerisable monomers may be any known monomers, for example selected from monomers of thermoset and thermoplast polymers and mixtures thereof, including monomers preferably selected from the group consisting of: an epoxy resin such as an epoxy resin derived from the mono or poly-glycidyl derivative of one or more of the group of compounds consisting of aromatic diamines, aromatic monoprimary amines, aminophenols, polyhydric phenols, polyhydric alcohols, polycarboxylic acids and the like; an addition-polymerisation resin, such as a bis-maleimide resin, acrylic, vinyl or unsaturated polyester; a formaldehyde condensate

resin, such as a formaldehyde-phenol resin, urea, melamine or phenol resin; a cyanate resin; and an isocyanate resin; polyaromatics such as polysulphones and polyethersulphones; monomers of natural polymers including carbohydrates, polypeptides and proteins including starch, celluloses, collagen, gelatin, dextrans, alginates, chitin and chitosan; and monomers of biodegradeable and/or biocompatible polymers such as polyesters including poly(lactic acid), poly(glycolic acid), polycaprolactone and the like, polyorthoesters, polyanhydrides, polyaminoacids and azo

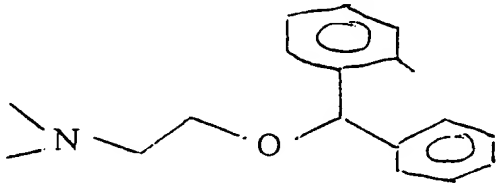
polymers, for example for the delivery of a pharmaceutical, veterinary product or agrochemical *in situ* .

In a further aspect of the invention there is provided a process for the preparation of compounds of the formula Iii:

(Iii) 

by the functional modification of a compound of formula I as hereinbefore defined to include additional groups R^1 and R^3 or the interconversion of one compound of formula I as hereinbefore defined to another compound of formula I as hereinbefore defined.

Preferably the compound of formula Iii as hereinbefore defined is a spatial, electronic or reactive analogue of a known pharmaceutical, veterinary product, or agrochemical, for example of a neuro active compound, such as the compound orphenadrine of formula:



for use in treating Parkinson's Disease or of cardiovascular or gastro-intestinal drugs, immunosuppresants, respiratory agents, musculoskeletal and joint disease drugs, immunological products and vaccines, pest control agents, plant growth control agents, plant disease control agents and the like.

In a further aspect of the invention there is provided the use of one or more compounds of formula I as hereinbefore defined in the preparation of a library of compounds comprising:

reacting one or more compounds of formula I as hereinbefore defined with one or more substrates which are supported or contained in solid or liquid phase each on an individual support or within an individual vessel; and

labelling the support or vessel with means to identify the synthetic history of the supported or contained compound.

The process for preparing a library of compounds may employ any techniques as known in the art of combinatorial chemistry.

In a further aspect of the invention there is provided a process for the preparation of a library of compounds of formula I as hereinbefore defined comprising:

reacting one or more compounds of formula IV as hereinbefore defined with a plurality of compounds of formula V as hereinbefore defined, and converting via compounds of formula II as hereinbefore defined to compounds of formula I as hereinbefore defined; and

optionally labelling the support or vessel with means to identify the synthetic history of the supported or contained compound.

In a further aspect of the invention there is provided a library of compounds of formula I, II or III as hereinbefore defined.

Preferably the library of compounds is suitable for any of the hereinbefore defined uses. The library may be provided in the form of a kit of sample boxes for the intended use. The library may contain two or more compounds, for example ten or more compounds, preferably comprises 50-1,000 compounds of any given formula as hereinbefore defined, optionally including synthetic history identification.

In a further aspect of the invention there is provided a pharmaceutical, veterinary product or agrochemical composition comprising a compound of formula I as hereinbefore defined or derivatives thereof together with suitable diluents, adjuvants, carriers and the like.

The invention is now illustrated in non limiting manner with reference to the examples and Table 1.

Ex	I	Z	R2	R2	R2	R3	R3	IV ester	III alcohol	II oxazolid -inone
1.1	4	H	CH3	CH3	H	Ph	Ph	Methyl 1	butanol 2	3
1.2	8	H	CH2Ph	H	H	Ph	Ph	ethyl 5	Butanol 6	7
1.3	12	H	H	H	H	Ph	Ph	Methyl 9	Butanol 10	11
1.4	15	H	C2H5	CH3	H	Ph	Ph	Methyl	Pentanol 13	14
1.5	18	H	IPr	H	H	Ph	Ph	Methyl	Pentanol 16	17

2.1	19	F	C2H5	CH3	H	Ph	Ph	Methyl	13	14
2.2	20	F	iPr	H	H	Ph	Ph	Methyl	16	17
2.3	21	F	-pyrrolidine-		H	Ph	Ph	Tet:	Tet:	Tet:

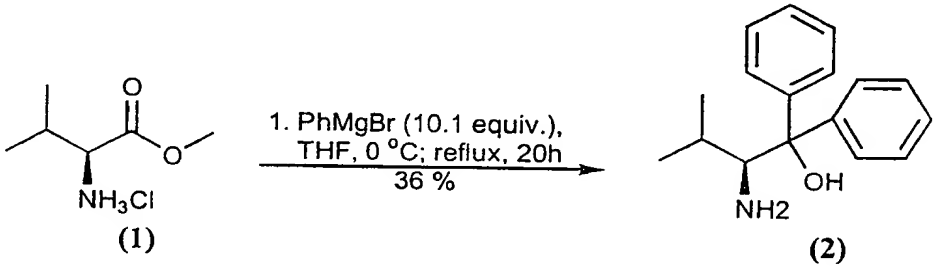
Examples - Synthesis of Novel Chiral Amines

1. Chiral Amines wherein Z is H

1.1 Synthesis of (S)-2-amino-1,1-diphenyl-3-methyl-1-butane (2)

Synthesis of (S)-2-amino-1,1-diphenyl-3-methyl-1-butanol (2)

The title compound (2) was readily prepared by the addition of L-valine methyl ester hydrochloride (1) to phenylmagnesium bromide, as depicted in **Scheme 1**, following the modified method described by Gawley[i] and Zhang (1996), and Itsuno[ii] *et al.* (1985).



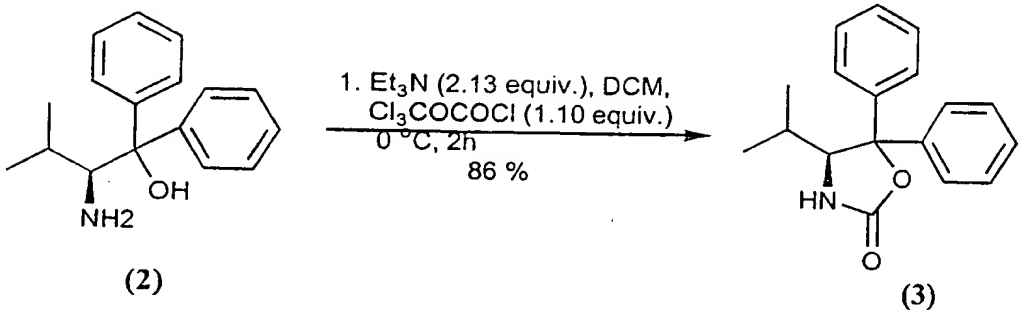
(1) (2)

Scheme 1

Purification over silica gel, gave (2) as a white solid in moderate yield (36 %).

Synthesis of (S)-4-isopropyl-5,5-diphenyl-2-oxazolidinone (3)

In the event, the title compound (3) was readily prepared by the cyclisation of aminoalcohol (2) with trichloromethyl chloroformate ($Cl_3COCOCl$) in the presence of triethylamine (Et_3N), as shown in **Scheme 2**, following the method described by Akiba[iii] *et al.* (1994).



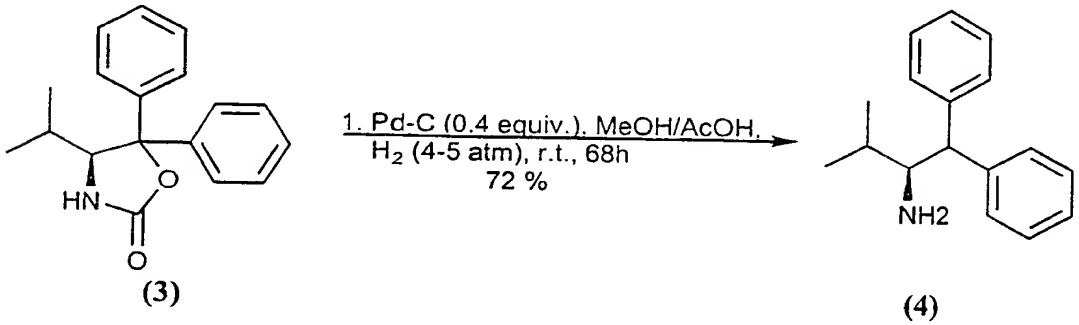
(2) (3)

Scheme 2

Upon work-up, the solid residue was loaded on to a sintered funnel and then washed with diethyl ether to obtain the title compound **(3)** as a white solid in good yield
(86 %).

Synthesis of (S)-2-amino-3-methyl-1,1-diphenylbutane (4)

In the presence of a catalytic amount of palladium on activated carbon, 2-oxazolidinone **(3)** was finally submitted to the hydrogenation in a mixture of AcOH and MeOH under 4-5 atm. pressure, as illustrated in **Scheme 3**.



(3) (4)

Scheme 3

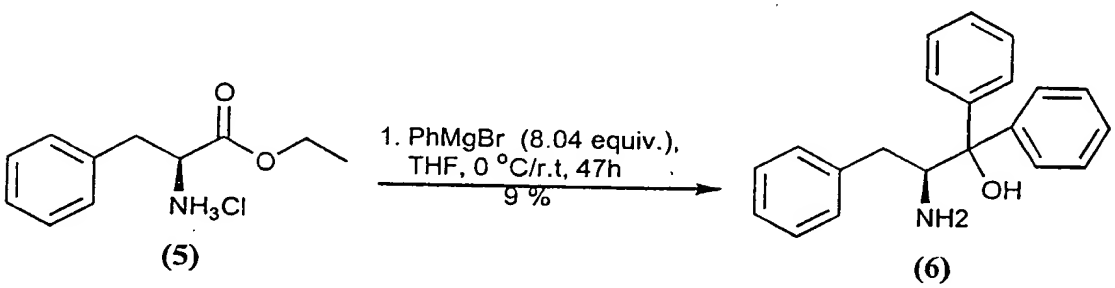
Upon filtration and re-crystallisation from petroleum ether, the title compound **(4)** was generated as a white solid in good yield (72 %).

1.2 Synthesis of (S)-2-amino-1,1,3-triphenyl-1-propane (6)

Synthesis of (S)-2-amino-1,1,3-triphenyl-1-propanol (6)

The title compound **(6)**, following the modified literature methods of Itsuno[ii,iv] *et al.* (1985), Weber[v] *et al.* (1995) and Dammast and Reißig[vi] (1993),

was readily prepared by the portionwise addition of L-phenylalanine ethyl ester hydrochloride **(5)** to phenylmagnesium bromide, as depicted in **Scheme 4**.



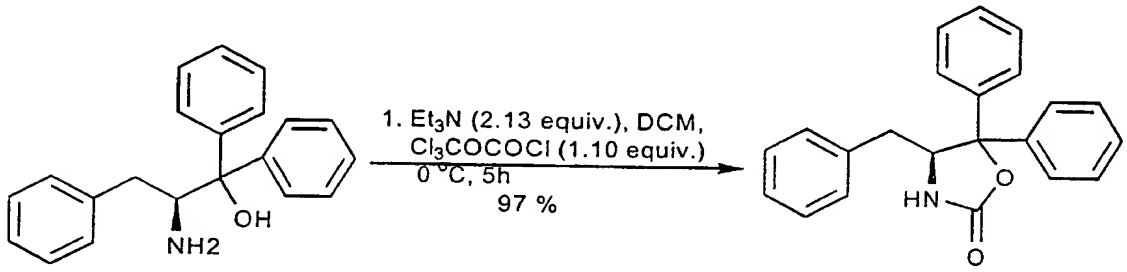
(5) **(6)**

Scheme 4

Recrystallisation gave the title compound **(6)** as a white solid in low yield (9 %).

Synthesis of (S)-4-benzyl-5,5-diphenyl -2-oxazolidinone (7)

In the event, the title compound **(7)** was readily prepared by the cyclisation of aminoalcohol **(6)** with trichloromethyl chloroformate ($Cl_3COCOCl$) in the presence of triethylamine (Et_3N), as shown in **Scheme 5**, following the method described by Akiba[iii] *et al.* (1994).



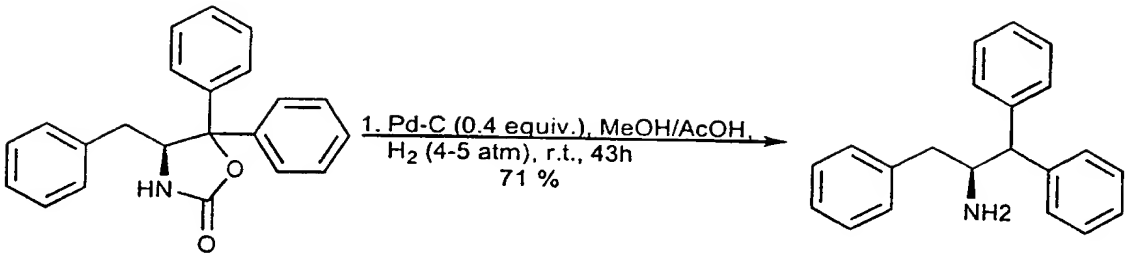
(6) **(7)**

Scheme 5

Upon work-up, the solid residue was loaded on to a sintered funnel and then washed with diethyl ether to obtain the title compound **(7)** as a white solid in excellent yield (97 %).

Synthesis of (S)-2-amino-1,1,3-triphenyl-propane (8)

In the presence of a catalytic amount of palladium on activated carbon, 2-oxazolidinone (7) was finally subjected to the hydrogenation in a mixture of AcOH and MeOH under 4-5 atm. pressure, as illustrated in **Scheme 6**.



(7) (8)

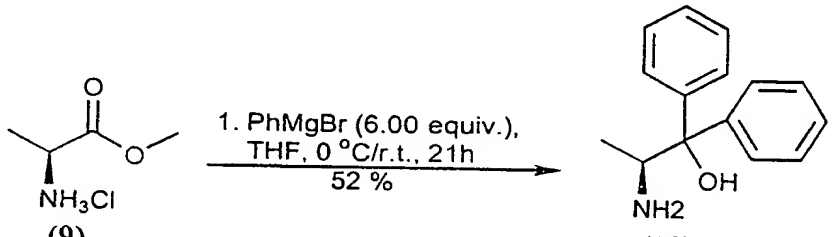
Scheme 6

Upon filtration and purification over silica gel, eluting with a 3:7 and 4:6 mixture of AcOEt and petrol, the title compound **(8)** was obtained as a light-brown solid in good yield (71 %).

1.3 Synthesis of (S)-2-amino-1,1-diphenyl-1-propanol (10)

Synthesis of (S)-2-amino-1,1-diphenyl-1-propanol (10)

The title compound **(10)**, following the literature methods of Itsuno[ii] *et al.* (1985), Weber[v] *et al.* (1995) and Dammast[vi] and Reißig (1993), was readily prepared by the portionwise addition of L-alanine methy ester hydrochloride **(9)** to phenylmagnesium bromide, as depicted in **Scheme 7**.



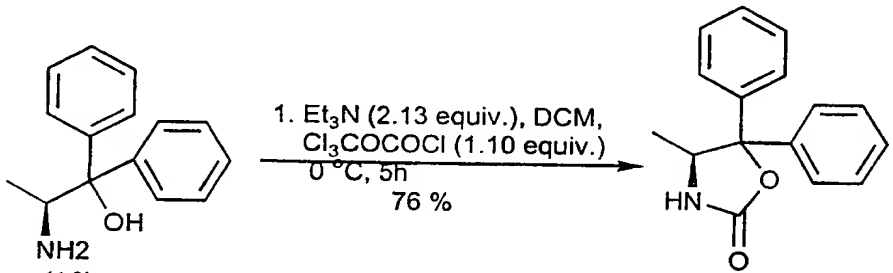
(9) (10)

Scheme 7

Flash column chromatography, eluting with dichloromethane and then further elution with a mixture of AcOEt and petrol, ranging from 15 % up to 100 %, gave the title compound **(10)** as a white solid in moderate yield (52 %).

Synthesis of (S)-4-methyl-5,5-diphenyl-2-oxazolidinone (11)

In the event, the title compound **(11)** was readily prepared by the cyclisation of aminoalcohol **(10)** with trichloromethyl chloroformate ($Cl_3COCOCl$) in the presence of triethylamine (Et_3N), as shown in **Scheme 8**, following the method described by Akiba[iii] *et al.* (1994).



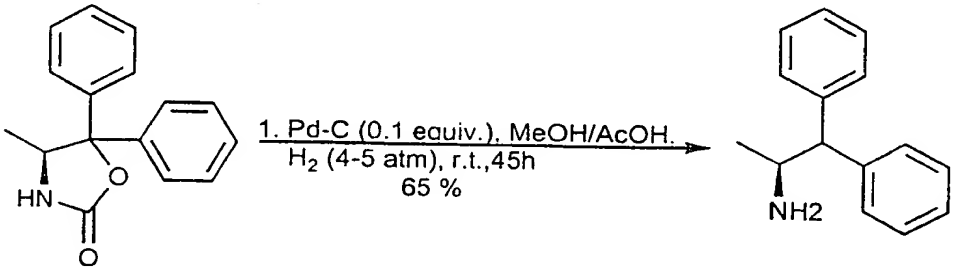
(10) **(11)**

Scheme 8

Upon work-up, the solid residue was loaded on to a sintered funnel and then washed with diethyl ether to obtain the title compound **(11)** as a white solid in good yield (76 %).

Synthesis of (S)-2-amino-1,1-diphenyl-propane (12)

In the presence of a catalytic amount of palladium on activated carbon, 2-oxazolidinone **(11)** was finally subjected to the hydrogenation in a mixture of AcOH and MeOH under 4-5 atm. pressure, as illustrated in **Scheme 9**.



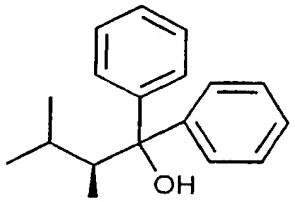
(11) **(12)**

Scheme 9

Upon filtration and purification by dry- flash column chromatography, eluting first with AcOEt, and then with a mixture of MeOH and AcOEt, ranging from 5 % up to 30 %, gave the title compound (12) as a white solid in moderate yield (71 %).

Experimental

1.1 (S)-2-amino-1,1-diphenyl-3-methyl-1-butanol (2)

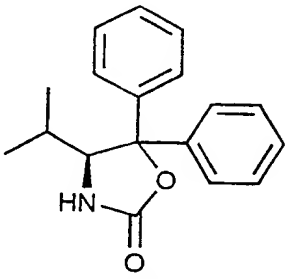


(2)

L-Valine methyl ester hydrochloride (9.9 g, 59.06 mmol) was added portionwise to a 1.0 M solution of phenylmagnesium bromide (108.8 g, 0.6 mol) in THF at 0 °C and heated at reflux for 20h. After quenching with crushed ice and NH_4Cl salt, the organic layer was separated, washed with brine and concentrated under reduced pressure. The resulting solid was treated with HCl (2.0 M, 100 ml) and then evaporated to dryness under reduced pressure. Impurities precipitated out as a white solid, when the amine hydrochloride salt was dissolved in hot MeOH and allowed to cool to room temperature. After removing the impurities by filtration, the filtrate was made basic with KOH (1.0 M) and the organics were extracted into diethyl ether (4x100 ml). Combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to obtain a crude product as a light brown solid. Purification over silica gel, eluting with a 1:4 and 1:1 mixture of ethyl acetate and petrol gave the title compound **(2)** (5.42 g, 36 %) as a white solid. m.p. 90-92 °C (lit[i] 94-95 °C). $[\alpha]_D^{25}$ = - 107.92° (c, 0.0424 in $CHCl_3$) (lit[ii]: - 127.7° (c, 0.639 in $CHCl_3$). δ_H 0.81 (3H, d, ^3J= 6.90 Hz, CH_3), 0.85 (3H, d, ^3J= 7.20 Hz), 1.67 (1H, ds, ^3J= 1.80 and 6.90 Hz, CH-Me_2), 3.76 (1H, d, ^3J= 2.10 Hz, CH-NH_2), 7.04-7.58 (10H, m, Ar). δ_C 16.3 and 23.2 (CH_3), 28.1 (CH-Me_2), 60.4 (CH-NH_2), 79.9 (C-OH), 125.7, 126.1, 126.5, 126.8, 128.2 and 128.6 (o-, m- and p-Ar), 145.1 and 148.2 (α-Ar). Anal. Calcld. for $C_{17}H_{21}NO$: C 79.96; H 8.29; N

5.48. Found: C 79.80; H 8.15; N 5.39. ir 3338 (OH and NH_2). m/e (CI-CH_4) 256 (MH^+, 14 %), 72 (100 %).

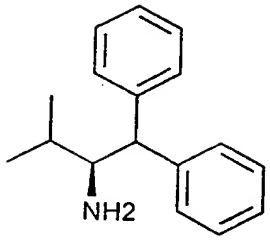
(S)-4-isopropyl-5,5-diphenyl-2-oxazolidinone (3)



(3)

Trichloromethyl chloroformate (2.71 g, 13.7 mmol) was added to a mixture of (S)-2-amino-3-methyl-1,1-diphenyl-1-butanol **(2)** (3.18 g, 12.45 mmol) and triethylamine (2.68 g, 26.52 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 2h at the same temperature and then poured into a brine solution (250 ml). The aqueous layer was made basic with NaOH pellets and organic products were extracted into AcOEt (5x200 ml). Combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was washed with diethyl ether to obtain the title compound **(3)** (3.03 g, 86 %) as a white solid. m.p. 250-251 °C (liti 250-251 °C). $[\alpha]_D^{25}$ = - 201.59° (c, 0.0252 in DMSO). δ_H (DMSO-d_6) 0.51 (3H, d, ^3J= 6.60 Hz, CH_3), 0.92 (3H, d, ^3J= 7.20 Hz, CH_3), 1.86 (1H, ds, ^3J= 2.10 and 6.60 Hz, CH-Me_2), 4.46 (1H, d, ^3J= 6.5 Hz, CH-NH_2), 7.24-7.72 (10H, m, Ar-H), 8.14 (1H, s, NH). δ_C 15.2 and 20.9 (CH_3), 29.8 (CH), 64.9 (CH-NHCO), 88.4 (C-O), 125.8, 126.2, 127.9, 128.4, 128.8 and 129.1 (Ar), 140.5 and 146.1 (α-Ar), 158.1 (C=O). Ir 3295 (NH_2), 1765 and 1745 (C=O). m/e (CI-NH_3) 282 (MH^+, 25 %), 299 (MNH_4^+, 8 %), 238 (96 %), 223 (100 %), 72 (100 %).

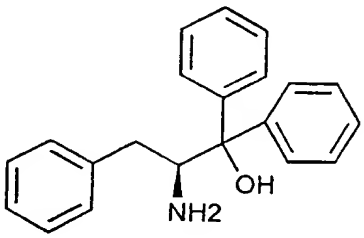
(S)-2-amino-3-methyl-1,1-diphenylbutane (4)



(4)

A solution of (S)-4-isopropyl-5,5-diphenyl-2-oxazolidinone (3) (2.9 g, 10.31 mmol) in MeOH/AcOH and a 10 % Pd (435 mg, 4.09 mmol) on activated carbon was shaken for 68h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered off over Hyflo Super Cell and organic solvents were evaporated under reduced pressure. The resulting residue was treated with HCl (2.0 M, 50 ml), stirred for 2h at room temperature, made basic with NaOH pellets, and saturated with K_2CO_3 and NaCl. Organic compounds were then extracted into AcOEt (3x 100 ml), dried over $MgSO_4/K_2CO_3$ and concentrated under reduced pressure to obtain a crude product. Re-crystallisation from petroleum ether gave the title compound **(4)** (1.79 g, 72 %) as a light-brown solid. m.p. 71-72 °C. $[\alpha]_D^{25} = -4.19°$ (c, 0.1097 in $CHCl_3$). δ_H 0.78 (3H, d, ^3J= 6.60 Hz, CH_3), 0.91 (3H, d, ^3J= 7.20 Hz, CH_3), 1.26 (2H, broad s, NH_2), 1.62 (1H, ds, $CHMe_2$), 3.45 (1H, dd, ^3J= 10.5 and 2.40 Hz, CH-NH_2), 3.70 (1H, d, ^3J= 10.5 Hz, CH-Ph_2), 7.00-7.40 (10H, m, Ar-H). δ_C 14.2 and 21.5 (CH3), 28.9 (CH-Me_2), 58.1 and 58.9 (CH-NH_2 and CH-Ph_2), 126.5, 126.7, 128.2, 128.5, 128.8 and 129.0 (o-, m- and p-Ar), 143.5 (2xα-Ar). Anal. Calcld for $C_{17}H_{21}N$: C 85.30; H 8.84; N 5.85. Found: C 85.12; H 8.91; N 5.96. ir 3361 (NH_2). m/e (CI-CH_4) 240 (MH^+, 8 %), 72 (100 %).

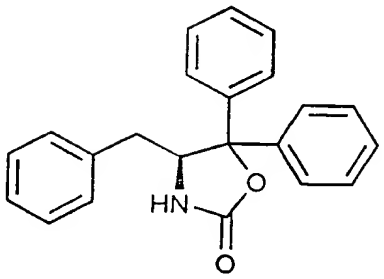
1.2 **(S)-2-Amino-1,1,3-triphenyl-1- propanol (6)**



(6)

L-Phenylalanine ethyl ester hydrochloride (9.9 g, 43.1 mmol) was added portionwise to a 1.0 M solution of phenylmagnesium bromide (63.46 g, 0.35 mol) in THF at 0 °C and stirred for 20h at room temperature. After quenching with crushed ice and concentrated HCl, the aqueous layer was separated and evaporated to dryness under reduced pressure. The resulting solid was washed with diethyl ether and AcOEt to obtain a white gummy HCl-salt. Upon basification with NaOH (1.0 M), organic products were extracted into diethyl ether and AcOEt, dried over $MgSO_4$, and concentrated under reduced pressure to obtain a crude product. Re-crystallisation from a mixture of AcOEt and diethyl ether gave the title compound **(6)** (1.16 g, 9 %) as a white solid. m.p. 141-142 °C (lit[ii] 144-145 °C; lit[vi] 143-144 °C). $[\alpha]_D^{25}$ = - 88.40° (c, 0.0181 in $CHCl_3$) (lit[ii]: - 88.50° (c, 0.604 in $CHCl_3$); lit[vi]: - 94.3° (c, 2.30 in $CHCl_3$). δ_H 2.38 (1H, dd, ^3J= 10.8 Hz, ^2J= 13.8 Hz, CH_2-Ph), 2.58 (1H, dd, ^3J= 2.4 Hz, ^2J= 13.8 Hz, CH_2-Ph), 4.11 (1H, dd, ^3J= 2.4 Hz, ^3J= 10.8 Hz, CH-NH_2), 7.06-7.62 (15H, m, Ar-H). δ_C 36.9 (CH_2-Ph), 58.4 (CH-NH_2), 78.7 (C-OH), 125.6, 126.0, 126.6, 126.7, 126.9, 128.4, 128.7, 128.8 and 129.3 (o-, m- and p-Ar), 139.8, 144.5 and 147.0 (α-Ar). ir 3365 (NH_2), 3320 (OH). m/e (CI-NH_3) 304 (MH^+, 30 %), 271 (100 %).

(S)-4-benzyl-5,5-diphenyl -2- oxazolidinone (7)

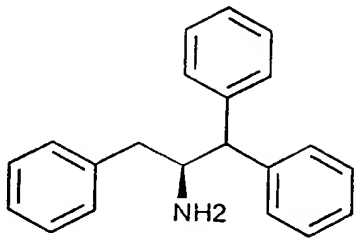


(7)

Trichloromethyl chloroformate (718 mg, 3.63 mmol) was added to a mixture of (S)-2-amino-1,1,3-triphenyl-1-propanol (6) (1.00 g, 3.30 mmol) and triethylamine (710 mg, 7.02 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 5h at the same temperature and then poured into a brine solution (150 ml). The aqueous layer was made basic with powdered K_2CO_3 and organics were extracted into dichloromethane (3x50 ml). The combined organic extracts were dried over $MgSO_4/K_2CO_3$ and concentrated under reduced pressure. The resulting crude product was washed with diethyl ether to obtain the title compound (7) (1.06 g, 97 %) as a white solid. m.p. 259-261 °C (lit ? °C). $[\alpha]_D^{25}$ = -241.94° (c, 0.0211 in DMSO), δ_H (DMSO-d_6) 2.18 (1H, dd, ^3J= 10.8 Hz, ^2J= 13.8 Hz, CH_2-Ph), 2.52 (1H, dd, ^3J= 3.6 Hz, ^2J= 13.8 Hz, CH_2-Ph), 4.67 (1H, dd, ^3J= 3.6 Hz, ^3J= 10.8 Hz, CH-NH_2), 6.90-7.60 (15H, m, Ar-H). δ_C 44.2 (CH_2-Ph), 50.5 (CH-NH), 94.1 (C-O), 130.5, 130.9, 131.5, 132.6, 132.8, 133.0, 133.1, 133.3 and 133.4 (o-, m- and p-Ar), 141.1, 143.4 and 146.5 (α-Ar), 163.7 (C=O). ir 3248 (NH_2), 1760 and 1725 (C=O). m/e (CI-NH_3) 330 (MH^+, 5 %), 347 (MNH_4^+, 6 %), 196 (100 %).

21

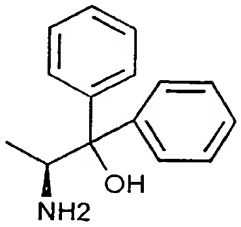
(S)-2-Amino-1,1,3-triphenyl-propane (8)



(8)

A solution of (S)-4-benzyl-5,5-diphenyl-2-oxazolidinone **(7)** (940 mg, 2.85 mmol) in MeOH/AcOH and a 10 % Pd (121 mg, 1.14 mmol) on activated carbon was shaken for 43h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered off over Hyflo Super Cell and organic solvents were evaporated under reduced pressure. The resulting residue was treated with HCl, stirred for 2h at room temperature, made basic with NaOH pellets, and saturated with K_2CO_3 and NaCl. Organics were then extracted into dichloromethane (4x 50 ml), dried over $MgSO_4/K_2CO_3$ and concentrated under reduced pressure to obtain a crude product. Purification over silica gel, eluting with a 3:7 and 4:6 mixture of AcOEt and petroleum ether, gave the title compound **(8)** (584 mg, 71 %) as a light-brown solid. m.p. 71-72 °C. $[\alpha]_D^{25}$ = -8.03° (c, 0.1046 in $CHCl_3$). δ_H 1.21 (2H, broad s, NH_2), 2.29 (1H, dd, ^3J= 9.6 Hz, ^2J= 13.5 Hz, CH_2-Ph), 2.79 (1H, dd, ^3J= 2.1 Hz, ^2J= 13.2 Hz, CH_2-Ph), 3.71 (1H, d, ^3J= 9.9 Hz, CH-Ph_2), 3.81 (1H, ddd, ^3J= 2.7, 9.9 and 12.6 Hz, CH-NH_2), 7.06-7.33 (15H, m, Ar-H). δ_C 41.9 (CH_2-Ph), 55.7 and 59.7 (CH-Ph_2 and CH-NH_2), 126.3, 126.5, 126.6, 128.1, 128.2, 128.4, 128.7, 128.8 and 129.1 (o-, m- and p-Ar), 139.7, 142.6 and 143.1 (α-Ar). ir 3387 (NH_2). m/e (CI-NH_3) 288 (MH^+, 100 %).

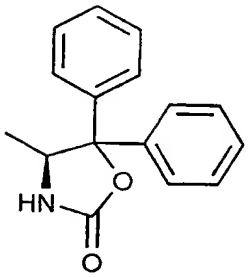
1.3 (S)-2-Amino-1,1-diphenyl-1- propanol (10)



(10)

L-Alanine methyl ester hydrochloride (9.9 g, 70.9 mmol) was added portionwise to a 1.0 M solution of phenylmagnesium bromide (78.0 g, 0.43mol) in THF at 0 °C and then heated under reflux for 21h. The reaction mixture was cooled to 0 °C, quenched with dropwise addition of saturated NH_4Cl, and stirred for 1h. After collecting insoluble products through the Buchner funnel, organic products were extracted into AcOEt (3x100 ml). The combined organic extracts were dried over $K_2CO_3/MgSO_4$, and concentrated under reduced pressure to obtain a crude product. Impurities were washed with dichloromethane over silica gel by means of dry-flash column chromatography, further elution with a mixture of AcOEt and petrol, ranging from 20 % up to100 %, gave the title compound **(10)** (1.16 g, 9 %) as a white solid. m.p. 100-101 °C (lit[ii,v] 100-102 °C). $[\alpha]_D^{25} = -85.59°$ (c, 0.0362 in $CHCl_3$) (lit[ii]: -82.38° (c, 0.814 in $CHCl_3$; lit[v]: -85.9° (c, 2.77 in $CHCl_3$). δ_H 0.94 (3H, d, ^3J= 6.30 Hz, CH_3), 1.23 (2H, broad s, NH_2), 4.15 (1H, q, ^3J= 6.30 Hz, CH-NH_2), 4.25 (1H, broad s, OH), 7.10-7.66 (10H, m, Ar-H). δ_C 17.4 (CH_3), 52.1 (CH-NH_2), 78.7 (C-OH), 125.7, 126.1, 126.6, 126.9, 128.2 and 128.7 (o-, m- and p-Ar), 145.0 and 147.2 (α-Ar). Anal. Calcld. for $C_{15}H_{17}NO$: C 79.26; H 7.54; N 6.16. Found: C 79.30; H 7.66; N 6.27. ir 3432 (OH), 3389 (NH_2). m/e (CI-NH_3) 228 (MH^+, 100 %).

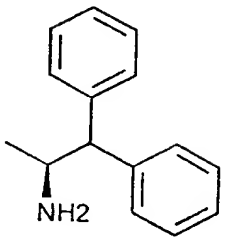
(S)-4-Methyl-5,5-diphenyl-2-oxazolidinone (11)



(11)

Trichloromethyl chloroformate (6.37 g, 32.19 mmol) was added to a mixture of (S)-2-amino-1,1-diphenyl-1-propanol (10) (6.65 g, 29.26 mmol) and triethylamine (6.31 g, 62.3 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 5h at the same temperature, poured into a brine solution (150 ml), and diluted with more dichloromethane. After collecting insoluble impurities through the Buchner funnel, the organic layer was separated and the aqueous layer was washed once with a mixture of dichloromethane and AcOEt. The combined organic extracts were dried over $MgSO_4/K_2CO_3$ and concentrated under reduced pressure. The resulting crude product was washed with diethyl ether, water, AcOEt and diethyl ether again, to obtain the title compound (11) (5.67 g, 76 %) as a white solid. m.p. 264-266 °C $[\alpha]_D^{25}$ = -279.71° (c, 0.0414 in DMSO). δ_H 0.82 (3H, d, ^3J= 6.30 Hz, CH_3), 4.65 (1H, q, ^3J= 6.0 Hz, CH-NH_2), 7.10-7.70 (10H, m, Ar-H), 7.93 (1H, broad s, NH). δ_C 19.6 (CH_3), 55.9 (CH-NH_2), 85.6 (C-O), 126.3, 126.4, 128.1, 128.6, 128.8 and 129.1 (o-, m- and p-Ar), 140.6 and 144.2 (α-Ar), 157.6 (C=O). ir 3254(NH), 1745 and 1725 (C=O). m/e (CI-NH_3) 254 (MH^+, 9 %), 271 (MNH_4^+, 55 %), 52 (100 %).

(S)-2-Amino-1,1-diphenyl-propane (12)

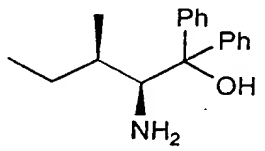


(12)

A suspension of (S)-4-methyl-5,5-diphenyl-2-oxazolidinone **(11)** (3.52 g, 13.90 mmol) in MeOH/AcOH and a 10 % Pd (148 mg, 1.39 mmol) on activated carbon was shaken for 45h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered off over Hyflo Super Cell and organic solvents were evaporated under reduced pressure. The resulting residue was treated with HCl (2M, 100 ml), stirred overnight at room temperature, made basic with NaOH pellets, and saturated with K_2CO_3. The organics were then extracted into diethyl ether (3x 100 ml), dried over $MgSO_4/K_2CO_3$ and concentrated under reduced pressure to obtain a crude product. Impurities were washed with AcOEt over silica gel by means of dry-flash column chromatography, and then further elution with a mixture of MeOH and AcOEt, ranging from 5 % up to 30 %, gave the title compound **(12)** (1.90 g, 65 %) as a white solid. m.p. 76-77 °C. $[\alpha]_D^{25}$ = - 19.32 (c, 0.10765 in $CHCl_3$). δ_H 1.04 (3H, d, ^3J= 6.30 Hz, CH_3), 1.31 (2H, broad s, NH_2), 3.55 (1H, d, J= 9.90 Hz, CH-Ph_2), 3.73 (1H, dq, ^3J= 6.30 and 10.20 Hz, CH-NH_2), 7.10-7.40 (10H, m, Ar-H). δ_C 22.4 (CH_3), 50.3 (CH-NH_2), 62.4 (CH-Ph_2), 126.5, 126.8, 128.2, 128.5, 128.7 and 129.0 (o-, m- and p-Ar), 143.3 and 143.7 (α-Ar). Anal. Calcld for $C_{15}H_{17}NO$: C 85.26; H 8.11; N 6.63. Found: C 85.10; H 8.08; N 6.36. ir 3343 (NH_2). m/e (CI-NH_3) 212 (MH^+, 100 %).

1.4 **(*S*)-α-(Diphenylmethyl)-α-[(*R*)-1-methylpropyl)-methylamine (15)**

(*2S,3R*)-2-Amino-1,1-diphenyl-3-methylpentan-1-ol (13)

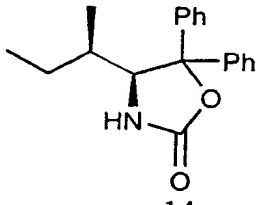


13

A 1 M solution of phenylmagnesium bromide (49.0 g, 0.27 mol) in THF was added dropwise to (*S*)-isoleucine methyl ester hydrochloride (9.8 g, 54.0 mmol) at 0 °C and then stirred for 17h at room temperature. The reaction mixture was cooled to 0 °C, quenched with dropwise addition of saturated NH_4Cl and then diluted with AcOEt and water until partition occurred. Organic products were extracted into AcOEt (3x50 ml), dried over $MgSO_4/K_2CO_3$ and concentrated to obtain a crude product. The crude product was dissolved in diethyl ether (150 ml), treated with concentrated HCl until all of the amine was converted to its HCl salt. The amine-HCl salt was stirred overnight, diluted with water until partition occured. The non-basic organics were extracted into diethyl ether (5x100 ml) and then the aqueous layer was made basic with NaOH pellets. After stirring for 4h, organic products were extracted into AcOEt (4x75 ml) and dried over $MgSO_4/K_2CO_3$. Concentration gave a crude product (6.1 g, 42 %) as a pale yellow solid. This contaminated with the amino ester derived from the starting material, however was used for the next step without further purification. A small amount of the crude product (1.1 g) was purified over silica gel by means of dry-flash column chromatography, eluting first with CH_2Cl_2, then with a mixture of AcOEt and petrol, increasing from 40 % up to 80 %. From this, a pure amino alcohol **13** (654 mg, 60 %) was obtained as a white amorphous solid. **m.p.** 128-129 °C (lit 135-136 °C). $[\alpha]_D^{25}$ = - 128.17° (c, 4.26 in $CHCl_3$) (lit: - 124.1° (c, 1.23 in $CHCl_3$)). δ_H 0.72 (3H, t, J= 7.2 Hz, CH_3), 0.94 (3H, d, J= 6.9 Hz, CH_3), 0.80-1.10 (1H, m, CH_2), 1.40-1.60 (1H, m, CH), 1.76-1.94 (1H, m, CH_2), 0.60-2.10 (3H, OH and NH_2), 3.85 (1H, d, J= 1.5 Hz, CH-NH_2), 7.10-7.70 (10H, m, Ar-H). δ_C 12.1 (CH_3-CH_2), 18.7 (CH_3-CH), 22.5 (CH_2), 34.8 (CH-Me), 60.9 (CH-NH_2), 79.6 (C), 125.5, 125.9, 126.1, 126.5, 127.8, 128.2,

144.9, 147.9 (Ar). ν_{max} (cm^{-1}): 3343, 3279 (N-H and O-H), 3085, 3023 (Ar C-H), 2959, 2926, 2873 (methyl and methylene C-H), 1589, 1491, 1447 (Ar C=C). **m/e** 270 (MH^+, 4 %), 252 (20 %), 86 (100 %).

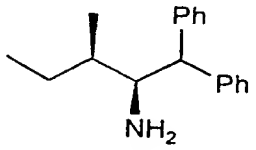
(*S*)-4-[(R)-1-Methylpropyl]-5,5-diphenyl-2-oxazolidinone 14



14

Trichloromethyl chloroformate (5.4 g, 27.3 mmol) was added to a mixture of (*S*)-2-amino-1,1-diphenyl-3-methylpentan-1-ol **13** (4.97 g of 60 %, 11.1 mmol) and triethylamine (5.3 g, 52.0 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 3h at 0 °C, then allowed to warm to room temperature for 18h. The mixture was then washed with HCl (3x100 ml) and water (2x100 ml) and dried over $MgSO_4$. Concentration gave a crude product, which was washed with diethyl ether to afford the title compound **14** (2.7 g, 83 %) as a white amorphous solid. **m.p.** 221-223 °C. $[\alpha]_D^{25}$ = - 243.9° (c, 4.33 in $CHCl_3$). δ_H 0.41 (3H, t, J= 7.2 Hz, CH_3), 0.80 (3H, d, J= 6.9 Hz, CH_3), 0.80-0.96 (1H, m, CH_2), 1.18-1.32 (1H, m, CH-Me), 1.34-1.50 (1H, m, CH_2), 4.27 (1H, d, J= 3.6 Hz, CH-NH), 6.98 (1H, s, NH), 7.10-7.50 (10H, m, Ar-H). δ_C 11.3 (CH_3-CH_2), 17.2 (CH_3-CH), 22.7 (CH_2), 36.3 (CH-Me), 66.1 (CH-NH), 89.5 (C), 125.9, 126.5, 127.7, 128.0, 128.3, 128.6, 139.3, 144.0 (Ar), 159.1 (C=O). ν_{max} (cm^{-1}): 3281, 3162 (N-H), 3058 (Ar C-H), 2980, 2960, 2933, 2877 (methyl and methylene C-H), 1760, 1725 (C=O), 1493, 1448 (Ar C=C), 1243 (C-O). **m/e** 313 (MNH_4^+, 6 %), 296 (MH^+, 8 %), 237 (100 %).

(*S*)-α-(Diphenylmethyl)-α-[(*R*)-1-methylpropyl)-methylamine 15

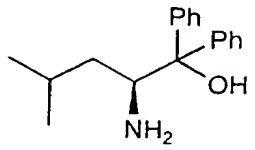


15

A suspension of (*S*)-4-*sec*-butyl-5,5-diphenyl-2-oxazolidinone 17 (2.3 g, 7.9 mmol) in MeOH/AcOH and a 10 % Pd (100 mg, 0.9 mmol) on activated carbon was shaken for 47h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered off over Hyflo Super Cell and solvents were evaporated. The resulting residue was treated with HCl until all of the amine was converted to its HCl salt, stirred overnight at room temperature and diluted with water until partition occurred. The non-basic organics were extracted into diethyl ether (2x100 ml) and the aqueous layer was made basic with NaOH pellets. Organic compounds were then extracted into CH_2Cl_2 (5x100 ml) and the combined extracts were dried over $MgSO_4$. Concentration gave a crude product, which was purified over silica gel by means of dry-flash column chromatography, eluting first with CH_2Cl_2, then with a mixture of AcOEt and petrol, ranging from 50 % up to 70 %. This afforded the title compound **15** (1.4 g, 71 %) as a white amorphous solid. **m.p.** 59-61 °C. $[\alpha]_D^{25}$ = -13.7° (c, 4.80 in $CHCl_3$). δ_H 0.76 (3H, t, J= 7.5 Hz, CH_3), 0.96 (3H, d, J= 6.9 Hz, CH_3), 1.00-1.18 (3H, broad s and m, NH_2 and CH_2), 1.28-1.42 (1H, m, CH-Me), 1.50-1.70 (1H, m, CH_2), 3.50 (1H, dd, J= 10.5 and 2.40 Hz, CH-NH_2), 3.87 (1H, d, J= 10.5 Hz, CH-Ph_2), 7.10-7.40 (10H, m, Ar-H). δ_C 11.2 (CH_3-CH_2), 16.7 (CH_3-CH), 20.4 (CH_2), 34.8 (CH-Me), 56.4 (CH-Ph_2), 58.4 (CH-NH_2), 125.2, 125.4, 127.0, 127.4, 127.5, 127.7 (Ar). **Accurate mass (CI):** Found 254.189998; Calculated for (MH^+) $C_{18}H_{24}N$ 254.190875 (3.4 ppm). ν_{max} **(cm^{-1}):** 3355 (N-H), 3082, 3065, 3024 (Ar C-H), 2959, 2931, 2872 (methyl and methylene C-H), 1598, 1494, 1450 (Ar C=C). **m/e (CI)** 254 (MH^+, 100 %).

1.5 (*S*)-α-(Diphenylmethyl)-α-isobutyl-methylamine 18

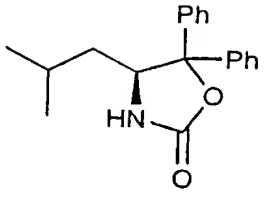
(*S*)-2-Amino-1,1-diphenyl-4-methylpentan-1-ol



16

A 1 M solution of phenylmagnesium bromide (96.1 g, 0.53 mol) in THF was added dropwise at 0 °C to (*S*)-leucine methyl ester hydrochloride (19.3 g, 0.11 mol) and then stirred for 17h at room temperature. The reaction mixture was cooled to 0 °C, quenched with dropwise addition of saturated NH_4Cl and then diluted with AcOEt and water until partition occurred. Organic products were extracted into AcOEt (3x100 ml), dried over $MgSO_4/K_2CO_3$ and concentrated to obtain a crude product. The crude product was dissolved in diethyl ether (400 ml), treated with concentrated HCl until all of the amine was converted to its HCl salt. The amine-HCl salt was stirred overnight and then diluted with water until partition occurred. The non-basic organics were extracted into diethyl ether (5x100 ml) and then the aqueous layer was made basic with NaOH pellets. After stirring for 4h, organic products were extracted into AcOEt (4x200 ml) and dried over $MgSO_4/K_2CO_3$. Concentration gave a crude product (13.7 g, 48 %) as a pale yellow solid. This contaminated with the amino ester of the unreacted starting material, however was used directly for the next step without further purification. A small amount of the crude product (1.31 g) was purified over silica gel by means of dry-flash column chromatography, eluting first with CH_2Cl_2, then a mixture of AcOEt and petrol, increasing from 30 % up to 55 %. From this, a pure amino alcohol **16** (852 mg, 65 %) was obtained as a white amorphous solid. **m.p.** 131-132 °C (lit 132-134 °C). $[\alpha]_D^{25} = -101.0°$ (c, 5.38 in $CHCl_3$) (lit: -95.1° (c, 1.01 in $CHCl_3$)). δ_H 0.79 (6H, dd, J= 7.20 and 7.80 Hz, CH_3), 0.86-1.80 (6H), 3.89 (1H, J= 9.6 Hz, CH-NH_2), 7.00-7.70 (10H, m, Ar-H). δ_C 21.1, 23.8, 25.1, 39.2, 54.3, 78.9, 125.4, 125.6, 126.1, 126.4, 127.8, 128.2, 144.3, 147.0 (Ar). ν_{max} (**cm-1**): 3337, 3268 (N-H and O-H), 3025 (Ar C-H), 2954, 2935, 2866 (methyl and methylene C-H), 1597, 1491, 1448 (Ar C=C). **m/e** 270 (MH^+, 5 %), 252 (M-OH, 11 %), 86 (100 %).

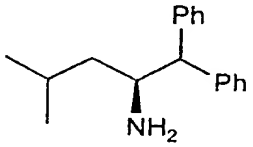
(*4S*)-4-Isobutyl-5,5-diphenyl-2-oxazolidinone 17



17

Trichloromethyl chloroformate (13.0 g, 65.8 mmol) was added to a mixture of (S)-2-amino-1,1-diphenyl-4-methylpentan-1-ol **16** (12.4 g of 65 %, 29.9 mmol) and triethylamine (12.7 g, 125.5 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 15h, allowing to warm to room temperature. The mixture was then washed with HCl (3x200 ml) and water (2x200 ml), and dried over $MgSO_4$. Concentration gave a crude product, which was washed with diethyl ether to afford the title compound **17** (7.9 g, 90 %) as a white solid. **m.p.** 212-214 °C. $[\alpha]_D^{25} = -286.1°$ (c, 4.32 in $CHCl_3$). δ_H 0.85 (3H, d, J= 6.6 Hz, CH_3), 0.91 (3H, d, J= 6.6 Hz, CH_3), 0.96-1.08 (2H, m, CH_2), 1.53-1.73 (1H, m, CH-Me_2), 4.57 (1H, dd, J= 10.5 and 3.60 Hz, CH-NH), 7.05 (1H, s, NH), 7.16-7.50 (10H, m, Ar-H). δ_C 20.8, 23.7, 24.9, 41.8, 58.8, 89.1, 125.9, 126.3, 127.6, 127.8, 128.1, 128.3, 139.3, 142.5 (Ar), 158.8 (C=O). ν_{max} **(cm-1):** 3261, 3160 (N-H), 2955, 2869 (methyl and methylene C-H), 1752, 17235 (C=O), 1495, 1447 (Ar C=C), 1251 (C-O). **m/e** 313 (MNH_4^+, 12 %), 296 (MH^+, 15 %), 237 (100 %).

(*S*)-α-(Diphenylmethyl)-α-isobutyl-methylamine 18



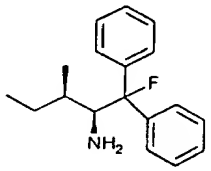
18

A suspension of (*S*)-4-isobutyl-5,5-diphenyl-2-oxazolidinone **17** (7.6 g, 25.6 mmol) in MeOH/AcOH and a 10 % Pd (282 mg, 2.6 mmol) on activated carbon was shaken for 93h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered off over Hyflo Super Cell and solvents were evaporated under reduced pressure. The resulting residue was treated with HCl until all of the amine was converted to its HCl salt, stirred overnight at room temperature and diluted with water until partitioned occurred. The non-basic organics were extracted into diethyl

ether (2x100 ml) and then the aqueous layer was made basic with NaOH pellets. Organics were then extracted into CH_2Cl_2 (5x 100 ml) and the combined extracts were dried over $MgSO_4$. Concentration gave the title product **18** (5.7 g, 87 %) as a white amorphous solid. **m.p.** 46-48 °C. $[\alpha]_D^{25} = -31.6°$ (c, 4.12 in $CHCl_3$). δ_H 0.86 (6H, dt, J= 6.60 and 2.10 Hz, CH_3), 1.00-1.50 (4H, m and broad s, CH_2 and NH_2), 1.66-1.86 (1H, m, CH), 3.61 (2H, broad s, CH-NH_2 and CH-Ph_2), 7.10-7.40 (10H, m, Ar-H). δ_C 21.8 and 24.7 (CH_3), 25.5 (CH), 45.6 (CH_2), 52.4 (CH-NH_2), 61.6 (CH-Ph_2), 126.9, 127.1, 128.8, 129.0, 129.2, 129.4, 143.8, 144.0 (Ar). **Accurate mass (CI):** Found 254.190200; Calculated for (MH^+) $C_{18}H_{24}N$ 254.190875 (2.7 ppm). ν_{max} **(cm-1):** 3368 (N-H), 3057, 3027 (Ar C-H), 2951, 2932, 2909, 2867 (methyl and methylene C-H), 1595, 1494, 1450 (Ar C=C). **m/e (CI)** 254 (MH^+, 100 %).

2. Chiral Amines wherein Z is F

2.1 (*S*)-α-(Fluorodiphenylmethyl)-α-[(*R*)-1-methylpropyl)-methylamine 19



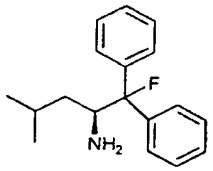
19

A solution of the oxazolidinone **14** (100mg, 0.34mmol) in CH_2Cl_2 (5ml) was carefully added to 30% HF-pyridine (2ml) (Olah's reagent) in a polythene bottle, and the contents were cooled to 0^0C. The solution was allowed to reach ambient temperature over 24 hours and was then poured into ice-cooled 2N aqueous ammonia solution (50ml). The organic layer was separated and the aqueous layer extracted into CH_2Cl_2 (3 x 30ml). The combined organic layers were dried over $MgSO_4$ and were then filtered and the solvent removed under reduced pressure. Purification by flash-column over silica gel chromatography (eluting with EtOAc/PetEt 1:4) generated the

fluorinated amine **19** as a white amorphous solid (23.1mg, 25%). On the basis of recovered starting material the yield is corrected to 53%.

$[\alpha]_D$=-32.3^0(MeOH, c = 0.6), m.p.: 76.9^{0}C; δ_H (400 MHz; $CDCl_3$): 7.45-7.16 (10H, m, $CH_{ar.}$), 3.82 (1H, qd, *J* 25.60 and 6.40, C**H**-NH_2), 1.65 (2H, s, NH_2), 1.03 (3H, *J* 6.80, CH_3); δ_F (376 MHz; $CDCl_3$): -174.91 (d, *J* 24.46)
HRMS (CI, M+H$^+$) found 272.1814. $C_{18}H_{22}NF$ requires 272.1815.

2.2 (*S*)-α-(Fluorodiphenylmethyl)-α-isobutyl-methylamine 20

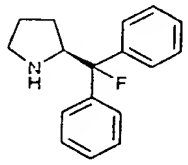


20

A solution of the oxazolidinone **16** (150mg, 0.51mmol) in CH_2Cl_2 (5ml) was carefully added to 30% HF-pyridine (1.5ml) (Olah's reagent) in a polythene bottle, and the contents were cooled to 0^{0}C. The solution was allowed to reach ambient temperature over 24 hours and was then poured into ice-cooled 2N aqueous ammonia solution (50ml). The organic layer was separated and the aqueous layer extracted into CH_2Cl_2 (3 x 30ml). The combined organic layers were dried over $MgSO_4$ and were then filtered and the solvent removed under reduced pressure. Purification by flash-column over silica gel chromatography (eluting with EtOAc/CH_2Cl_2, 1:4) generated the fluorinated amine 14 as a white amorphous solid (61mg, 44%). On the basis of recovered starting material the yield is corrected to 61%.

$[\alpha]_D$=-48.78°(MeOH, c= 1.2); m.p.: 84^{0}C; δ_H (400 MHz; $CDCl_3$): 7.50-7.26 (10H, m, $CH_{ar.}$), 3.72 (1H, ddd, *J* 26.0, 10.4 and 2.0, C**H**-NH_2), 1.85 (1H, m, C**H**$(CH_3)_2$), 1.51 (2H, s, NH_2), 1.35 (1H, m, C**H**$_a$H$_b$), 1.18 (1H, m, CH$_a$**H**$_b$), 0.87 (6H, t, *J* 6.4, 2C**H**$_3$; δ_F (376 MHz; $CDCl_3$): -174.1 (d, *J* 30.12); m/z (EI): 251 (5%, M-HF), 208 (26, [M-HF]-$CH(CH_3)_2$), 194 (8, [M-HF]-$CH_2CH(CH_3)_2$); HRMS (CI, M+H$^+$) found 272.1812. $C_{18}H_{22}NF$ requires 272.1815.

2.3 (S)-2-(Fluorodiphenylmethyl)-pyrrolidine 21



21

A solution of the oxazolidinone (200mg, 0.7mmol) in CH_2Cl_2 (5ml) was carefully added to 30% HF-pyridine (2ml) (Olah's reagent) in a polythene bottle, and the contents were cooled to 0^0C. The solution was allowed to reach ambient temperature over 24 hours and was then poured into ice-cooled 2N aqueous ammonia solution (50ml). The organic layer was separated and the aqueous layer extracted into CH_2Cl_2 (3 x 30ml). The combined organic layers were dried over $MgSO_4$ and were then filtered and the solvent removed under reduced pressure. Purification by flash-column over silica gel chromatography (eluting with EtOAc/petrol, 6:4) generated the fluorinated amine 14 and a viscous oil (55.8mg, 31%).

$[\alpha]_D$ = -8.08° (MeOH, c 7.4), δ_H (400 MHz; $CDCl_3$): 7. 47-7.16 (10H, m, $CH_{ar.}$), 4.14 (1H, td, *J* 28.40 and 7.20, **CH**), 3.02-2.95 (1H, m, CH_AH_B-NH), 2.85-2.77 (1H, m, $CH_A\mathbf{H_B}$-NH), 1.81-1.20 (2H, m, **NH** and $2\mathbf{CH_2}$); δ_F (376 MHz; $CDCl_3$): -171.02 (d, *J* 27.47). m/z (CI): 256 (76%, M+1), 236 (100, [M-HF]+1); HRMS (C1, $M+H^+$) found 256.1499. $C_{17}H_{18}NF$ requires 256.1502.

R. E. Gawley and P. Zhang, *J. Org. Chem.*, **1996**, 61, 8103.

1. S. Itsuno, M. Nakano, K. Miyazaki, H. Masuda, K. Ito, A. Hirao and S. Nakahama, *J. Chem. Soc., Perkin Trans. I*, **1985**, 2039.

2. T. Akiba, O. Tamura, M. Hashimoto, Y. Kobayashi, T. Katoh, K. Nakatani, M. Kamada and S. Terashima, *Tetrahedron*, **1994**, 50 (13), 3905.

3. S. Itsuno, M. Nakano, K. Miyazaki, K. Ito, A. Hirao, M. Owa and S. Nakahama, *J. Chem. Soc., Perkin Trans. I*, **1985**, 2615.

4. E. Weber, C. Reutel, C. Foces-Foces and A. L. Llamas-Saiz, *J. Phys. Org. Chem.*, **1995**, 8, 159.

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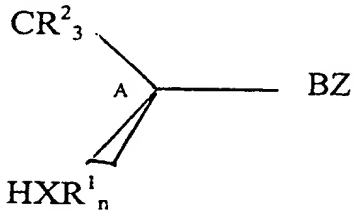
CLAIMS

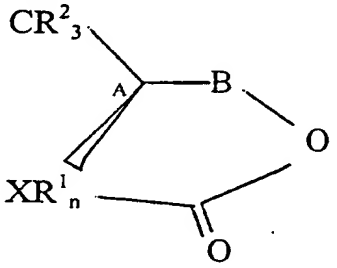
1. Process for the preparation of chiral compounds of formula I:

(I)



comprising contacting a compound of formula II:

(II)



with a source of hydrogen or halide;

wherein A is a chiral centre;

X is selected from oxygen, sulphur and nitrogen;

n is selected from 0 and 1 and is equal to the valence of X less 2;

Each R^1 is independently selected from hydrogen, straight chain and branched, saturated and unsaturated C_{1-8} hydrocarbon optionally substituted by one or more hydroxy, halo, aryl, cyclo C_{1-8} alkyl and the like;

B is a fragment CR^3_2 wherein each R^3 is independently selected from hydrogen, halo, azides and cyanides; straight and branched chain, saturated and unsaturated C_{1-4} alkyl, alkenyl and alkynyl and aryl, each optionally substituted by hydroxy, halo, saturated

or unsaturated C_{1-4} alkyl, alkenyl or alkynyl, aryl, cyclo C_{1-6} alkyl, carbonyl, carboxyl, amino, amido, (thio)ether, haloalkyl, silylalkyl and the like;

Z is hydrogen or halogen;

each R^2 is independently selected from hydrogen, straight chain and branched, saturated and unsaturated C_{1-8} alkyl, optionally substituted by hydroxy, halo, aryl, cyclo C_{1-6} alkyl, carbonyl, carboxyl, amino, amido, (thio)ether and the like; and

one of R^1 and one of R^2 together may form an alkylene group as part of a heterocyclic ring;

with the proviso that when X is nitrogen, n is 1, one of R^1 and two of R^2 are hydrogen, BZ is $CHPh_2$, the other R^1 and R^2 do not form together a five membered heterocyclic (pyrrolidone) ring.

2. Process as claimed in Claim 1 wherein X is nitrogen whereby n is 1.

3. Process as claimed in any one of Claims 1 and 2 wherein B is a fragment CR^3_2 wherein R^3 is selected from ethenyl, propenyl ethynyl and propynyl, optionally substituted phenyl.

4. Process as claimed in any one of Claims 1-3 wherein B is a group as hereinbefore defined wherein at least one and preferably both of R^3 are aryl.

5. Process as claimed in any one of Claims 1-4 wherein Z is selected from hydrogen, chloro and fluoro.

6. Process as claimed in Claim 5 wherein R^2 is selected from optionally hydroxy, halo, alkoxy substituted branched and straight chain C_{1-6} alkyl, including methyl, ethyl, i-propyl, i-butyl, t-butyl; and aryl including phenyl and benzyl.

7. Process as claimed in any one of Claims 1-6 wherein X is nitrogen wherein n is 1 and R^1 does not form a cyclic ring with one of R^2 or R^1 is H, and R^2 is other than H, i.e. the compound is a primary amine.

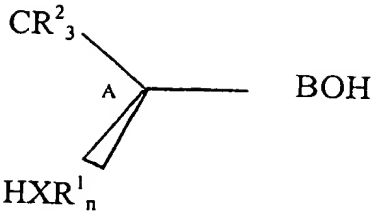
8. Process as claimed in any of Claims 1-7 conducted in the presence of a catalyst which is homogeneous or heterogeneous or of an agent which is gaseous or liquid.

9. Process as claimed in Claim 8 wherein the catalyst is a hydrogenation catalyst comprising a metal selected from the transition metals of Group VIII of the Periodic Table of the Elements optionally in the presence of or including additional catalytic components or catalytic supports such as C.

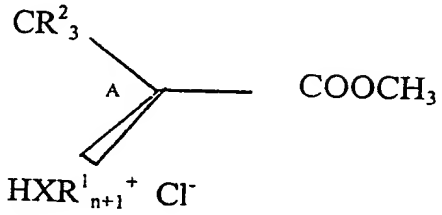
10. Process as claimed in Claim 8 wherein the agent is a fluorination agent comprising a source of fluorine associated with an activating component for example liquid phase HF and a carrier.

11. Process as claimed in any of Claims 1 to 10 for the preparation of pharmaceutical, veterinary product, agrochemical and polymeric compounds and libraries of such compounds, and their synthetic intermediates.

12. Process as claimed in any of Claims 1-11 wherein a compound of formula II is obtained from compounds of formula III:

(III) 

And a compound of formula III as hereinbefore defined is obtained by reaction of a compound of formula IV:

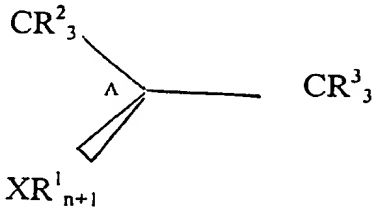
(IV) 

with a compound of formula V:

(V) R^2MgBr.

13. Novel intermediate of the formula II, III, IV, or V as defined in Claim 12.

14. Process as claimed in any of claims 1 to 13 comprising in an additional stage the modification or interconversion of a compound of formula I to a compound of the formula Iii:

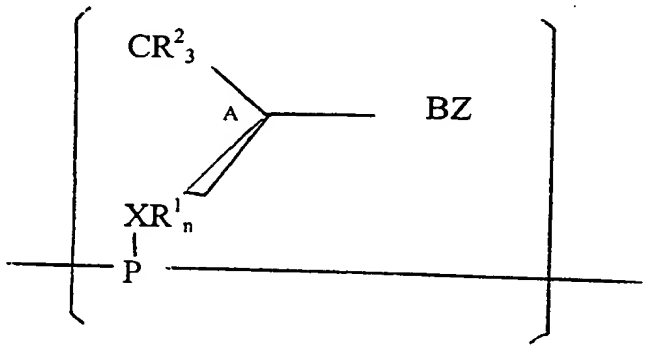
(Iii) 

by the functional modification of a compound of formula I as hereinbefore defined to include additional groups R^1 and R^3 or the interconversion of a compound of formula I as hereinbefore defined.

15. Compound of the formula I as hereinbefore defined in any of Claims 1 to 7 wherein A, B, Z and R^1 are as hereinbefore defined, X is N and n is 1 with the exception that R^2 is not phenyl or benzyl when R^1 is hydrogen, BH is phenyl or CH_3 and Z is H.

16. Process for the preparation of enantiomerically pure chiral polymer comprising a repeating unit of the formula Ii:

(Ii)



wherein P is derived from a polymerisable monomer or oligomer and X, R^1, R^2, B, Z and A are as hereinbefore defined;

comprising coupling a compound of formula I as hereinbefore defined with a monomer or oligomer and subsequently polymerising.

17. Process as claimed in Claim 16 wherein a polymerisable monomer is selected from the group consisting of: an epoxy resin; an addition-polymerisation resin; a formaldehyde condensate resin; a cyanate resin; and an isocyanate resin; polyaromatics; monomers of natural polymers including carbohydrates, polypeptides and proteins including starch, celluloses, collagen, gelatin, dextrans, alginates, chitin and chitosan; and monomers of

biodegradeable and/or biocompatible polymers including poly(lactic acid), poly(glycolic acid), polycaprolactone, polyorthoesters, polyanhydrides, polyaminoacids and azo polymers; and mixtures thereof.

18. Polymer as defined in Claim 17.

19. Polymer as defined in Claim 17 as a delivery agent for a pharmaceutical, veterinary product or agrochemical *in situ*.

20. Use of one or more compounds of formula I as hereinbefore defined in the preparation of a library of compounds.

21. Process for the preparation of a library of compounds of formula I as hereinbefore defined comprising:

reacting one or more compounds of formula IV as hereinbefore defined with a plurality of compounds of formula V as hereinbefore defined, and converting via compounds of formula II as hereinbefore defined to compounds of formula I as hereinbefore defined; and

optionally labelling the support or vessel with means to identify the synthetic history of the supported or contained compound.

22. Library of compounds of formula I, II or III as hereinbefore defined.

23. Pharmaceutical, veterinary product or agrochemical composition comprising a compound of formula I, Ii or Iii as hereinbefore defined with suitable diluents, adjuvants, carriers and the like.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/04031

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07B53/00 C07C209/68 C07C211/27 C07C211/29 C07D207/10
C07B61/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07B C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 09 143173 A (SHIRATORI PHARMACEUTICAL CO., LTD., JAPAN) 3 June 1997 (1997-06-03) page 3-4 ---	13,15
X	HINTERMANN, TOBIAS ET AL: "A useful modification of the Evans auxiliary. 4-Isopropyl-5,5- diphenyloxazolidin-2-one" HELV. CHIM. ACTA (1998), 81(11), 2093-2126 , XP002134506 page 2093 -page 2095	1,13,15
X	* see on page 2099 footnote 16) * --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 April 2000	17/04/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bader, K

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GIBSON C L ET AL: "A Study of 4-Substituted 5,5-Diaryl Oxazolidin-2-ones as Efficacious Chiral Auxiliaries" TETRAHEDRON LETTERS,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 39, no. 37, 10 September 1998 (1998-09-10), pages 6733-6736, XP004132590 ISSN: 0040-4039 page 6734	13,15

X	TAMURA O ET AL: "SYNTHETIC STUDIES ON THE KEY COMPONENT OF THE NEW GENERATION OF QUINOLONECARBOXYLIC ACID, DU-6859 1. SYNTHESIS OF (1R,2S)-2-FLUOROCYCLOPROPYLAMINE BY THE USE OF OPTICAL RESOLUTION" TETRAHEDRON,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 50, no. 13, 28 March 1994 (1994-03-28), pages 3889-3904, XP000575878 ISSN: 0040-4020 cited in the application page 3906	13
A	page 3913	1

X	BAILEY D J ET AL: "A short synthesis of (S)-2-(diphenylmethyl)pyrrolidine, a chiral solvating agent for NMR analysis" TETRAHEDRON: ASYMMETRY,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 8, no. 1, 9 January 1997 (1997-01-09), pages 149-153, XP004015186 ISSN: 0957-4166 cited in the application	1-3,5-9, 11-15
X	PREPARATION OF COMPOUND 4 ON PAGE 151	1

X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US YANG, XIAO-WU ET AL: "Convenient synthesis of (S)-.alpha.,.alpha.'-diphenyl-2-pyrrolidinemethanol" retrieved from STN Database accession no. 127:278113 XP002134513 abstract & GAODENG XUEXIAO HUAXUE XUEBAO (1997), 18(6), 911-913 ,	13,15

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate. of the relevant passages	Relevant to claim No.
X	RAO, A. V. RAMA ET AL: "Enantioselective catalytic reduction of ketones with new four-membered oxazaborolidines: application to (S)-tetramisole" TETRAHEDRON: ASYMMETRY (1992), 3(7), 859-62 , XP002134507 the whole document	13
X	GAWLEY, ROBERT E. ET AL: "1-Magnesiotetrahydroisoquinolyloxazolines as Chiral Nucleophiles in Stereoselective Additions to Aldehydes: Auxiliary Optimization, Asymmetric Synthesis of (+)-Corlumine, (+)-Bicuculline, (+)-Egenine, and (+)-Corytensine, and Preliminary 13C NMR Studies of 1-Lithio- and 1-Magnesiotetrahydroisoquinol" J. ORG. CHEM. (1996), 61(23), 8103-8112 , XP002134508 cited in the application SEE THE EXAMPLES	13,15
X	DELAUNAY, DOMINIQUE ET AL: "A new route to oxazolidinones" J. CHEM. SOC., PERKIN TRANS. 1 (1994), (20), 3041-2 , XP002134509 the whole document	13,15
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X	ALVERNHE, GERARD ET AL: "Fluorination of amino alcohols and hydroxyaziridines by Olah's reagent" J. CHEM. RES., SYNOP. (1983), (10), 246-7 , XP002134510	13,15
A	the whole document	1
X	WADE, TAMSIR N.: "Preparation of fluoro amines by the reaction of aziridines with hydrogen fluoride in pyridine solution" J. ORG. CHEM. (1980), 45(26), 5328-33 , XP002134511	13,15
A	page 5330	1
X	ALVERNHE, G. ET AL: "Synthesis of.alpha.,.beta.-fluoro amines and.alpha.-fluoro ketones by action of hydrofluoric acid on aziridines and azirines" TETRAHEDRON LETT. (1978), (52), 5203-6 , XP002134512	13,15
A	page 5204	1

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	KNOLKER H -J ET AL: "Synthesis of Chiral Oxazolidin-2-ones and Imidazolidin-2-ones via DMAP-Catalyzed Isocyanation of Amines with Di-tert-butyl Dicarbonate" TETRAHEDRON LETTERS,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 39, no. 51, 17 December 1998 (1998-12-17), pages 9407-9410, XP004144213 ISSN: 0040-4039 page 9408 ---	13,15
X,P	O'HAGAN D ET AL: "A short synthesis of (S)-alpha-(diphenylmethyl)alkyl amines from amino acids" TETRAHEDRON: ASYMMETRY,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 10, no. 6, 26 March 1999 (1999-03-26), pages 1189-1192, XP004164869 ISSN: 0957-4166 the whole document -----	1-23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/04031

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 99 /04031

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-23 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search over the whole breadth of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely Compounds of formula I with X=N, n=1 and B= -C(Ph)2 and Z= -F; as supported by the description on pages 29-31.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/04031

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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